A MINIMUM COST AND RISK MITIGATION APPROACH FOR BLOOD COLLECTION

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A MINIMUM COST AND RISK MITIGATION APPROACH FOR BLOOD COLLECTION

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To my family,

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SUMMARY

Due to the limited supply and perishable nature of blood products, effective management of blood collection is critical for high quality healthcare delivery. Whole blood is typically collected over a 6 to 8 hour collection window from volunteer donors at sites, e.g., schools, universities, churches, companies, that are a significant distance from the blood products processing facility and then transported from collection site to processing facility by a blood mobile.

The length of time between collecting whole blood and processing it into cryoprecipitate ("cryo"), a critical blood product for controlling massive hemorrhaging, cannot take longer than 8 hours (the 8 hour collection to completion constraint), while the collection to completion constraint for other blood products is 24 hours. In order to meet the collection to completion constraint for cryo, it is often necessary to have a "mid-day collection"; i.e., for a vehicle other than the blood mobile to pickup and transport, at extra cost, whole blood units collected during early in the collection window to the processing facility.

In this dissertation, we develop analytical models to: (1) analyze which collection sites should be designated as cryo collection sites to minimize total collection costs while satisfying the collection to completion constraint and meeting the weekly production target (the non-split case), (2) analyze the impact of changing the current process to allow collection windows to be split into two intervals and then determining which intervals should be designated as cryo collection intervals (the split case), (3) insure

that the weekly production target is met with high probability.

These problems lead to MDP models with large state and action spaces and constraints to guarantee that the weekly production target is met with high probability. These models are computationally intractable for problems having state and action spaces of realistic cardinality.

We consider two approaches to guarantee that the weekly production target is met with high probability: (1) a penalty function approach and (2) a chance constraint approach. For the MDP with a penalty function approach, we first relax a constraint that significantly reduces the cardinality of the state space and provides a lower bound on the optimal expected weekly cost of collecting whole blood for cryo while satisfying the collection to completion constraint. We then present an action elimination procedure that coupled with the constraint relaxation leads to a computationally tractable lower bound. We then develop several heuristics that generate sub-optimal policies and provide an analytical description of the difference between the upper and lower bounds in order to determine the quality of the heuristics.

For the multiple decision epoch MDP model with a chance constraint approach, we first note that a straightforward application of dynamic programming cannot always lead to an optimal policy. We then restrict the model to a single decision epoch and obtain the optimal policy for a single decision epoch. Building upon this idea, we propose a computationally tractable rolling horizon procedure to determine a sub-optimal policy for the multiple decision epoch problem. We also present a simple greedy heuristic based on ranking the collection intervals by mid-day pickup cost per unit of expected cryo collected, which results in a competitive sub-optimal solution and leads to the development of a practical decision support tool (DST). Using real data from the American Red Cross (ARC), we estimate that this DST reduces total cost by about 30% for the non-split case and 70% for the split case, compared to the current practice. Initial implementation of the DST at the ARC Southern regional manufacturing and service center supports our estimates and indicates the potential for significant improvement in current practice.

CHAPTER I

INTRODUCTION

1.1 Cryo Collection Problem

Each day, more than 44,000 blood donations are needed in the U.S., accounting for a total of 30 million annual blood component transfusions [2]. The demand for blood transfusions continues to rise due to an increasing prevalence of chronic diseases, ageing population, and recent advancements in major therapies such as heart surgeries and organ transplants [42]. The margin between blood need and transfusable blood product availability has been critically tight [68], and warnings of blood shortages have received extensive media coverage recently (see for e.g., [1, 50]). Despite national awareness campaigns and intense media attention, less than 5% of the eligible U.S. population donate blood [42]. In addition, the increase in demand has outpaced the increase in donations, with donations increasing annually by about 3% and demand growing at 6% [1].

Due to the limited supply and perishable nature of blood products, effective management of blood collection is critical for high quality healthcare delivery. Blood shortages and stock outs may cause serious problems in hospital operations and can result in morbidity and mortality. The most recent national blood collection and utilization survey reports that about 10.3% of U.S. hospitals reported experiencing inadequate blood supply for nonsurgical blood needs, and 3.3% reported cancelation of elective surgeries due to blood inventory shortages in 2008. Yet during the same year, about 4.3% of all components of blood processed for transfusions became outdated [68].

Blood collection operations are complex processes. Blood can be collected from donors either through automated blood collection (apheresis) or through regular whole-blood (WB) donation, the latter being significantly more common [28]. WB is collected from donors at fixed collection sites such as blood centers and at mobile collection sites through blood drives. Once collected, WB can be separated into different components, including red blood cells, platelets, plasma, and cryoprecipitate. Each of these components has different collection, production, and storage constraints. For example, while platelets have the shortest shelf life after processing (5-7 days), cryoprecipitate has the strictest time constraint between collection and processing (only 8 hours).

Cryoprecipitate (also called "cryoprecipitated antihaemophilic factor", or for short "cryo") is the main source of fibrinogen in the U.S. and plays a critical role in clotting and controlling massive hemorrhaging [51]. Cryo is prepared by thawing a unit of fresh-frozen plasma (FFP) and concentrating the clotting factors. Cryo is used in the treatment of massive trauma and many major diseases, including metastasized cancers, cardiac diseases, hepatic failures, organ transplants, and acquired immune deficiency syndrome (AIDS). Due to the advancements in major surgeries and treatments, the demand for FFP, the raw material for cryo preparation, has been increasing rapidly [66]. For example, from 2000-2010, the use of FFP has increased tenfold and grew to more than 2.4 million units used annually in the U.S. [35].

The Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB) require that cryo can only be prepared from FFP [47]. While the length of time between collection and completing the production process is 24 hours for non-cryo blood products, this bound is only 8 hours for cryo. That is, the time needed to transport, process, and freeze cryo cannot exceed 8 hours from the time of collection [13]. This tight collection-to-completion constraint significantly complicates cryo collection and production planning and poses managerial challenges and practical ramifications for major blood suppliers with geographically remote collection sites [27].

In this thesis, we describe and analyze a regional level cryo collection problem motivated by our collaboration with the American Red Cross (ARC) Southern regional manufacturing and service center (RMSC) and present our analysis and results proposed for improving operations in practice. For the past three years, we have been collaborating with the ARC Southern RMSC, which is responsible for all ARC blood service activities in the Southern US region and serves more than 120 hospitals. The ARC Southern RMSC management team has asked the authors to develop methods and practical algorithms to aid in planning weekly cryo collection schedules in the region. Such collection schedules were expected to ensure that the weekly cryo collection targets are achieved with a high probability, while total collection costs are minimized.

1.1.1 Ground Realities and Important Problem Dynamics

Working closely with the ARC Southern RMSC, we have uncovered the following ground realities. WB is collected at fixed and mobile sites. The majority of the collection sites (about 80%) are mobile sites, which typically collect blood between 9AM-5PM for cryo and non-cryo products. The locations of mobile collection sites and their associated collection time windows are determined months in advance, based on demand forecasts, how recently the mobile site has been visited, and convenience to the host site. The assigned mobile collection vehicle leaves the RMSC for its collection site in time to start collection at the beginning of the collection window. At the end of the collection window, the mobile collection vehicle is packed up and departs for going back to the RMSC.

The number of units of a specific blood product to manufacture is decided weekly at the end of the preceding week. In particular, RMSCs are given a weekly target for cryo units just prior to the beginning of the week. WB collected for cryo production must be collected in special bags (called triple bags) and has an 8 hour collection-to-completion constraint, while all other blood products are collected in so-called (and less expensive) double bags and have a 24 hour collection-to-completion constraint.

Operationally, at least a two-day notice is required so that boxes can be packed with a sufficient number of the appropriate type of bag for the mobile collection vehicles. Thus, two days prior to actual collection, each mobile site is designated as either a cryo site or a non-cryo site, boxes holding the collection bags are packed with either triple or double bags, and at the beginning of the day of collection, the assigned mobile collection vehicles are loaded with the appropriate boxes. Excess storage is not possible on the mobile collection vehicles due to capacity and weight constraints, thus prohibiting the mobile collection vehicles from carrying additional boxes that would permit same-day determination of what blood products can be collected at any given mobile site.

Transport from the mobile collection sites to the RMSC is provided by the blood collection vehicles at the end of the day (at no extra charge). Such a delivery is called *an end-of-day delivery*. If the end-of-day delivery cannot satisfy the eight hour collection-to-completion constraint for a cryo site, then the RMSC schedules additional transportation from the site to the RMSC at some time during the collection window. Such transport is called *a mid-day pickup* and incurs an extra expense. Due to unpredictable traffic patterns and the time-sensitive nature of cryo, a mid-day pickup vehicle collects WB units for cryo (hereinafter referred to as "cryo units") only from one mobile site per trip and returns back to the RMSC for processing (i.e. no vehicle routing). If no mid-day pickups were scheduled, typically the weekly cryo collection target could not be achieved. Alternatively, scheduling an excessive number of mid-day pickups would unnecessarily increase transportation costs.

Unexpected transport delays and/or processing delays at the RMSC can cause a violation of the collection-to-completion constraint for both mid-day pickups and end-of-day deliveries. When the collection-to-completion constraint is violated, the WB collected in triple bags can be used for another blood product (e.g., plasma, red blood cells). However, since triple bags cost more than double bags, an unnecessary charge is incurred and more importantly the weekly cryo target is less likely to be achieved. If the weekly target is missed, the RMSC may need to quickly (and at considerable extra expense) transport cryo units from other regions, which may not be possible if supplies of cyro in other regions are also limited. Similarly, if a mobile collection unit packed with triple bags no longer needs to collect blood for cryo (e.g., the weekly target has already been achieved), then the cost of a mid-day pickup can be eliminated, although the extra expense of using triple bags for non-cryo blood products cannot be eliminated.

Lastly, we remark that the number of cryo units collected at a mobile collection site is uncertain because 1) scheduled donors may not show up, 2) many of the donors are walk-ins and are not scheduled, and 3) there is no guarantee blood collected in a triple bag will result in successful production of cryo. Some collected blood units are discarded because of failing to pass the safety tests and errors made during collection [59].

1.2 Literature Review on Blood Supply Chain

There is a large body of literature on supply chain management of blood products. This literature can be broadly categorized as: a) inventory management, b) distribution of the processed blood products, and b) collection planning.

Most of the literature on blood supply chain management focuses on inventory management decisions. Several mathematical models have been built to aid in inventory management decisions and provide answers to many questions, including the following: what inventory levels should a hospital blood bank set [14, 57, 34, 53, 40, 17, 29], what ordering policies would minimize blood wastage [26, 79], what is the optimal target levels for various blood components at blood banks [38, 11, 36, 69], how to jointly replenish and issue inventory when there is age-differentiated demand and inventory substitution [39, 23], how should collaboration and coordination between hospitals and regional centers be organized to improve the efficiency of the supply chain [32], how to better manage blood supply-chains with geographic information-systems-based analytics [21], and what factors affect stock level and wastage at hospital blood banks [54].

In addition, several studies have considered blood allocation and redistribution decision making. These decisions include allocation of processed blood components to various hospitals in the region [56, 58, 30], development of redistribution and reallocation policies among small and large hospitals [22], development of blood rotation policies [43], and location-allocation decisions [63, 52]. Some of these modeling-based allocation policies have been successfully implemented in practice (see for example [15]).

We refer the reader to [41] and [4] for detailed reviews of the recent literature on blood inventory management and distribution (see also [57, 49] and [55] for reviews of the earlier work in these areas) and now focus on the literature that has considered collection planning decisions. While there is a vast literature on blood inventory management and product distribution, research focusing on blood collection planning has been limited. Below, we summarize a handful of studies that considered blood collection decisions. [19] developed a Markovian-based population model to reduce seasonal imbalances between blood supply and demand. Key to this planning model was to forecast blood collections on a given day, which was automated using a computer-assisted planning system. This planning model was implemented by two regional blood suppliers. [78] studied the problem of identifying from which sites to shuttle blood and the routing of these shuttles for each given day. They assumed known and constant collections at each site and modeled this problem as a vehicle routing problem with time windows (VRPTW) with the objective to minimize the transportation costs. [25] also considered a similar problem to that of [78], and addressed the case when multiple pickups at a single site were possible. Similar to [78], they also assumed known and constant collections, and modeled this problem as a special VRPTW with the aim of finding the minimum cost tours and allocate appropriate transport devices to take back all the blood. Both [78] and [25] had similar motivations to our work in the sense that they considered the time-sensitive nature of FFP products upon collection. However, unlike [78] and [25] which focused on daily collection schedules assuming set daily targets and known and constant collections at each sites, we focus on the weekly collection schedules and consider sequential nature of these decisions as well as the uncertainty in collections in our analyses, which appear to be major factors in weekly collection decisions.

1.3 Overview

To our knowledge, this is the first study that considers optimizing cryoprecipitate collections. Our contributions in this thesis are two-fold. From an application and societal impact viewpoint, we have applied mathematical modeling and analysis techniques to determine WB collection policies for cryo, a critically important blood product. We have translated some of these results into a decision support tool (DST) for operational application by the American Red Cross' Southern RMSC. Using real data from the ARC, we estimate that the use of the proposed DST reduces total cost by about 30% and 70% for the non-split and split cases respectively, compared with the current practice. Initial implementation of the DST at the ARC Southern RMSC supports our estimates and indicates the potential for significant improvement in current practice. From a methodological viewpoint, we propose general approaches for determining lower and upper bounds on the optimal value function and an action elimination rule. Both of these approaches consider the probability of achieving the weekly cryo collection target. Further, we determine an analytical description of the difference between the upper and lower bounds on the cost function of the MDP model, thus determining a measure of sub-optimal policy quality. These results lead to near-optimal solutions (Heuristics 1.1 through 1.3, IP1.1 and IP1.2) and provide benchmark statistics to assess the performance of Heuristic 2.1, a competitive and computationally very efficient algorithm that is currently being used in practice.

The remainder of this dissertation is organized as follows. In Chapter 2, we develop the MDP model with a penalty function and describe our analytical results and algorithm development for computational analysis. In Chapter 3, we consider a variety of methods to find the sub-optimal policy resulting from the MDP model to satisfy a chance constraint. In Chapter 4, we present numerical results of a case study, including data analysis, computation improvement and policy evaluation. Finally, in Chapter 5, we summarize our findings and conclude.

CHAPTER II

MARKOV DECISION PROCESS WITH A PENALTY FUNCTION

2.1 Introduction

In this chapter we begin by modeling the cryo collection problem as an MDP with a terminal cost and present the corresponding optimality equations. We then note that the MDP is intractable to solve due to its large state and action spaces. We present several structural results for the solutions of the optimality equations and relax the constraint that an interval must be designated either a cryo interval or a non-cryo interval at least two days in advance in order to determine lower bounds on the solutions of the optimality equations. We then present an action elimination procedure and a result that accelerates this action elimination procedure, develop a family of heuristics based on the policy that results from the lower bound, and finally determine a bound on the difference between the resultant upper and lower bound.

2.2 Model Formulation

As indicated earlier, the Southern RMSC designates sites as either cryo or non-cryo sites so as to minimize the expected total cost of collecting cryo throughout the week, while achieving the collection target and satisfying the operational constraint that a site must be designated either a cryo site or a non-cryo site at least two days in advance. Total cost over the week is comprised of mid-day transport costs and the additional cost of triple bags. We assume that the capacity of the RMSC production facility is large enough to process all of the cryo units collected in a day in the region. This is a reasonable assumption because production capacity constraints are taken into account when collection sites are scheduled months in advance.

The current practice, which we call the *non-split model*, is to designate a site as either a cryo or non-cryo site. However, the ARC management team is considering another possible way to structure cryo collection operations with the intent of further reducing expected total cost. We refer to this alternative model as the *split model*, where the collection window of each site is split into two intervals. In the split model, instead of collecting WB for either cryo or non-cryo throughout the entire collection window, WB could be collected for either cryo or non-cryo throughout each of the intervals. Thus, for example, WB could be collected for non-cryo products during the earlier interval and for cryo during the later interval. WB collected for cryo during the earlier interval would require a mid-day pickup. However, WB collected for cryo during the later interval could be transported back to the production facility by the mobile collection vehicle without an additional transport charge. Note that such a split would permit at least some cryo to be collected without the cost of a mid-day pickup. We remark that if we constrain both intervals of a collection window to be either cryo intervals or non-cyro intervals, then the split model becomes the non-split model. Hence, we consider the non-split model as a special case of the split model. Without loss of generality, we describe the split model as follows.

Weekly plan: A weekly plan is comprised of the number of cryo units that needs to be collected and processed (the weekly "target"), the list of the mobile collection sites where WB collection will take place for each day of the week, the time interval during which collection will take place (i.e., the "collection window"), and projected amount of WB collections for each site. The weekly target, the locations of the sites throughout the week, and the collection windows as well as the projected amount of collections for each of the sites are determined in advance and are assumed fixed.

Decision Variables & Information Pattern: Let $d \in \{1, \cdots, 6\}$ denote the day of the week excluding Sunday, where $1 =$ Monday, $\cdots$, $6 =$ Saturday. For a given day d, assume there are N collection sites. Let the random variable Y_n be the number of units collected at site $n \in \{1, \cdots, N\}$. Let $\lambda_n \in [0, 1]$ be the fraction of the collection window available for a mid-day pickup at collection site n. Thus, assuming there is a mid-day pickup, this pickup would occur at time $t_B + \lambda_n(t_E - t_B)$, where t_B and t_E are respectively the beginning and ending times of the collection window. Therefore, the collection window is comprised of two intervals, the *first* interval $(t_B, t_B + \lambda_n(t_E - t_B))$ and the *second* interval $(t_B + \lambda_n(t_E - t_B), t_E)$. For example, if the collection window for collection site n is from $11am$ to $4pm$, $\lambda_n = 0.4$, and there is a mid-day pickup, then the mid-day pickup would depart at $1pm$ and transport all units collected from $11am$ to $1pm$ from collection site n to the production facility. Let the random variables Y_{1n} and Y_{2n} be the number of units collected before and after, respectively, the mid-day departure time. Then, the total number of collected units on day n $Y_n = Y_{1n} + Y_{2n}$, where the realization of Y_{1n} becomes available at the time of the mid-day departure, and the realization of Y_{2n} becomes available at the end of the collection window.

There are two types of decisions to make, the *daily collection plan* and the *actual collection schedule*. The daily collection plan determines how the boxes carrying the bags for blood collection are packed for the bloodmobiles. The daily collection plan for day d must be decided at least two days before day d and remains fixed thereafter. Let $a^d = \{(a_{1n}, a_{2n}), n = 1, \cdots, N\}$ be the daily collection plan for day d, where for collection site n:

- If $a_{1n} = 1$, then pack cryo bags for Y_{1n} possible units to be collected during the first interval and a possible mid-day pickup.

- If $a_{1n} = 0$, then pack non-cryo bags for Y_{1n} possible units to be collected during the first interval, thus eliminating the possibility of collecting for cryo during the first interval.

- If $a_{2n} = 1$, then pack cryo bags for Y_{2n} possible units to be collected during the second interval for the end-of-day pickup

- If $a_{2n} = 0$, then pack non-cryo bags for Y_{2n} possible units to be collected during the second interval, thus eliminating the possibility of collecting for cryo during the second interval.

Let $a = \{(a'_{1n}, a'_{2n}), n = 1, \cdots, N\}$ be the actual collection schedule for day d. The actual collection schedule can be determined in the morning of day d prior to the departure of the bloodmobiles. At this point, we can decide whether or not we actually will use blood collected in cryo bags for cryo production. Blood cannot be used for cryo production unless it is collected in cryo bags; however, blood collected in cryo bags can be used for any blood product. Thus, the actual collection schedule for day d, $a = \{(a'_{1n}, a'_{2n}), n = 1, \cdots, N\}$, is constrained by the earlier determined daily collection plan, $a^d = \{(a_{1n}, a_{2n}), n = 1, \cdots, N\}$, as follows: $a'_{in} \leq a_{in}$, for all $i \in \{1, 2\}$ and for all $n = 1, \cdots, N$, i.e., $a \leq a^d$. We remark that since cryo bags are (modestly) more expensive than non-cryo bags, there is incentive to pack cryo bags only when the likelihood is high that the cryo bags actually will be used for cryo. However, deciding that blood to be collected in cryo bags during a first interval will not be used for cryo production eliminates the need for and cost of a mid-day pickup.

System Dynamics: Let the random variable D^d represent the total number of cryo units collected from all sites on day d. Assume N collection sites for day d, and let $\mathcal{D}$ be the sample space for D^d. Then, for actual collection schedule $a = \{(a'_{1n}, a'_{2n}), n =$

$1, \cdots, N\}$ on day d, $D^d = \sum_n (Y_{1n} a'_{1n} + Y_{2n} a'_{2n})$. Let $P^d(D|a)$ be the probability that $D^d = D$. Let z^d be the number of cryo units needed to be collected for the rest of the week, starting from the morning of day $d \in \{1, \cdots, 5\}$. Then, $z^{d+1} = z^d - D^d$ for all d. Note that z^1 is the weekly target and that the inequality $z^6 \leq 0$ represents meeting or exceeding the weekly target.

Cost Structure: Let $c^d(a^d, a)$ be the expected total cryo collection cost during day $d \in \{1, \cdots, 5\}$, given daily collection plan a^d and actual collection schedule a. Two costs are accrued: (1) the cost difference between a cryo bag and a non-cryo bag when a cryo bag is used for collection and (2) the cost of a mid-day pickup. Let Δ be the difference in cost between a cryo bag and a non-cryo bag, and let C_n be the cost of a mid-day pickup at collection site n. Then, for $a^d = \{(a_{1n}, a_{2n}), n = 1, \cdots, N\}$ and $a = \{(a'_{1n}, a'_{2n}), n = 1, \cdots, N\}$, $c^d(a^d, a) = \Delta \sum_n E(D(a^d)) + \sum_n C_n a'_{1n}$, where E is the expectation operator.

Optimality Equations: The actual collection schedule for day d is selected knowing z^d, a^d, and a^{d+1}, except for Friday, when a^5 is selected knowing z^5 and a^5. Before Monday, a^1, a^2, and a^3 are determined. Since the actual collection schedule for Monday can be determined when a^1, a^2, and a^3 are determined, Mondays actual collection schedule and a^1 can be identical. We assume that the daily collection plans a^4 and a^5 are selected on the mornings of Tuesday and Wednesday, respectively.

- On Saturday, no blood production occurs, therefore there are no decisions to make. However, it is known whether or not the weekly target was met. We let $v^6(z^6)$ represent the penalty function for not achieving the weekly target.

- At the beginning of Friday, we know a^5 and how much of the weekly target has yet to be collected, z^5. Note that Friday's collection plan, a^5, is determined two days in advance on Wednesday, and the only permissible modification to this plan on the day of collection is that cryo collection can be canceled for the part of the day (either first half or the second half), or the entire day, i.e. $a \leq a^5$. The optimality equation then becomes:

$$v^5(a^5, z^5) = \min_{a \leq a^5} \left\{ c^5(a^5, a) + \sum_{D \in \mathcal{D}} P^5(D|a) v^6(z^5 - D) \right\}, \tag{1}$$

where $v^5(a^5, z^5)$ is the minimum total expected cost to be accrued throughout the remainder of the week, and a is the actual collection decision made on Friday morning, given a^5 and z^5.

- At the beginning of Thursday, we know a^4, a^5, and z^4. Note that similar to Friday, on Thursday morning, the only control action we have is that we can make some modifications to Thursday's plan to finalize the actual collection schedule, a based on a^4. Let $v^d(a^d, a^{d+1}, z^d)$, where $d \in \{1, \cdots, 4\}$, represent the minimum total expected cost to be accrued throughout the remainder of the week from day d onwards, given a^d, a^{d+1}, and z^d. The optimality equation then becomes:

$$v^4(a^4, a^5, z^4) = \min_{a \leq a^4} \left\{ c^4(a^4, a) + \sum_{D \in \mathcal{D}} P^4(D|a) v^5(a^5, z^4 - D) \right\}. \tag{2}$$

- At the beginning of Wednesday, we know a^3, a^4, and z^3. On Wednesday morning, in addition to making any necessary modifications to the original collection plan for Wednesday which is made on Monday (i.e., a^3), we should also determine the collection plan for Friday (i.e. a^5). The optimality equation then becomes:

$$v^3(a^3, a^4, z^3) = \min_{a \leq a^3} \min_{a^5 \in A} \left\{ c^3(a^3, a) + \sum_{D \in \mathcal{D}} P^3(D|a) v^4(a^4, a^5, z^3 - D) \right\}. \tag{3}$$

- Similar to Wednesday, at the beginning of Tuesday, we know a^2, a^3, and z^2, and need to determine a and a^4. The optimality equation then becomes:

$$v^2(a^2, a^3, z^2) = \min_{a \le a^2} \min_{a^4 \in A} \left\{ c^2(a^2, a) + \sum_{D \in \mathcal{D}} P^2(D|a) v^3(a^3, a^4, z^2 - D) \right\}. \quad (4)$$

- Lastly, prior to the beginning of the week, we know the weekly target z^1, and need to determine Monday's, Tuesday's, and Wednesday's collection schedules, i.e. a^1, a^2, a^3, respectively. Note that for Monday, there is no reason to adjust a^1, and hence $c^1(a^1, a) = c^1(a^1, a^1)$ and $P^1(D|a) = P^1(D|a^1)$. The optimality equation then becomes:

$$v^1(a^1, a^2, z^1) = \min_{a^1, a^2, a^3 \in A} \left\{ c^1(a^1, a^1) + \sum_{D \in \mathcal{D}} P^1(D|a^1) v^2(a^2, a^3, z^1 - D) \right\}. \quad (5)$$

2.3 Analytical Results

Regarding the computational implications of the optimality equations (Equations 1-5), we note, for example, that the Wednesday optimality equation (Equation 3) has an action space cardinality of 4^{10} and a state space cardinality of $4^{10} \times 4^{10} \times 10^3$, which is approximately 1.1×10^{15}, when $N = 10$ and $z^1 = 10^3$ (typical values for N and z^1, based on historical data provided by ARC). This analysis indicates that a direct application of dynamic programming is intractable for realistically sized problems. Therefore, we derive some analytical results to help with the computation. We begin with the following reasonable assumptions.

Assumption 1 *The penalty function $v^6(z^6)$ is non-negative, non-decreasing, and equals 0 when $z^6 \le 0$.*

This assumption implies that (1) as the size of the unmatched weekly target (i.e. weekly target minus actual collection) increases, the penalty increases, and (2) there is no penalty for over-collection. The first implication is clearly reasonable. The second implication is also reasonable because over-collecting cryo units up to 300 units per week is acceptable to the ARC management team and our model ensures that no more than 300 cryo units will be over-collected per week because of the following reasons: (1) our analysis of the real data shows that just end-of-day collections themselves are not sufficient for meeting the weekly collection target (and hence mid-day pickups are needed), and (2) the projected amount of collection per mobile site is almost always less than 200 units. Note that to minimize the costs, the model will schedule as few mid-day pickups as possible meeting the target, which guarantees that $z^6 \geq -200$.

Assumption 2 *The fraction of a collection window for a mid-day pickup, λ_n, is* 0.5 *for all n. The probability distributions for blood collection per unit time for each of the two intervals are identical.*

This first assumption in Assumption 2 implies that we divide the collection window in two equal intervals for all sites, and set the mid-day pickup time as the middle. This assumption was made after consulting ARC management and insures that whole blood collected for cryo in the first half of the collection window will satisfy the 8 hour collection to completion constraint. The second assumption is also reasonable because we have not found significant differences between blood collections from the first and second intervals.

2.3.1 Structural Results

When the size of a problem is large, which is often referred to as "the curse of dimensionality", dynamic programming (DP) becomes computationally intractable. There are several papers (e.g., [76, 33, 5, 16]) that use discretized or aggregated state spaces and convergence approaches for problems with uncountable or large countable state spaces or with complex transition and/or cost structures. One natural approach is to aggregate states by collecting similiar states into subsets (e.g., [48, 64, 3, 31, 9]).

Another approach is to decompose large DPs into smaller related DPs, and use the solutions of smaller DPs to obtain a good solution for the original DP (e.g., [77, 18, 44]). Some general state space reduction methods can be found in [74] and [75].

We now present an important structural result (Proposition 1) that helps to reduce the size of the state and action spaces. In particular, based on Assumption 1, we show that v^d is isotone in z^d for all d, implying that for each day d, the more units of cryo that are needed to meet the weekly target, the greater the expected cost to meet the weekly target. This structural result is inherited by the lower bounds presented in Proposition 4 and is a key condition for the action elimination result in Proposition 5. Unless included in the main text, all proofs are presented in the appendix.

Proposition 1 $v^5(a^5, z^5)$ *is non-decreasing in* z^5 *and* $v^d(a^d, a^{d+1}, z^d)$ *is non-decreasing in* z^d *for all* $d \in \{1, 2, 3, 4\}$.

Next, we show that it is not optimal to assign $\alpha_n = 1$ and $\beta_n = 0$ as daily collection plan or daily collection schedule, because end-of-day pickup ($\beta_n = 1$) can be regarded as a free ride, while mid-day pickup ($\alpha_n = 1$) requires additional transport cost. This result allows us to restrict number of states and actions considered in one site from 4 to 3.

Proposition 2 *If* $a = \{(\alpha_n, \beta_n), n = 1, \cdots, N\}$ *is such that* $\exists\ i,\ s.t.\ \alpha_i = 1, \beta_i = 0$, *then* a *can never be the optimal daily collection plan, or optimal actual collection schedule.*

The following result implies that the optimal actual collection schedule will not cancel an end-of-day delivery (because there is no value added in cancelling an end-of-day pickup for cryo), thus reducing the cardinality of the action space that needs to be searched. We remark that for the non-split model, it is not possible to cancel a mid-day pickup without canceling the concomitant end-of-day delivery, and hence the following result applies only to the split model.

Proposition 3 *Let* $a^d = \{(\alpha_n, \beta_n), n = 1, \cdots, N\}$*, and* $\underline{a^d} = \{(0, \beta_n), n = 1, \cdots, N\}$ *for any* $d \in \{1, 2, 3, 4, 5\}$*. Then, in the split model, the action set* $\{a \leq a^d\}$ *can be replaced by* $\{\underline{a^d} \leq a \leq a^d\}$ *in Optimality Equations (1)-(5) in searching for the actual collection schedule for day d in order to determine* $v^d(a^d, a^{d+1}, z^d)$*,* $d = 2, \cdots, 4$*, and* $v^5(a^5, z^5)$*.*

Propositions 2 and 3 can reduce state and action space cardinality, but not to the point of tractability. Hence, we turn our attention to seeking a good sub-optimal policy and begin by determining a computationally tractable lower bound on the $\{v^d\}$. Determination of this lower bound also produces a useful sub-optimal actual collection schedule.

2.3.2 Model Relaxation

Lower Bounds: We now present lower bounds on the v^d by removing the constraint that an interval must be designated either a cryo interval or a non-cryo interval at least two days in advance. Let $h^d(z^d, a, v) = c^d(a, a) + \sum P^d(D|a)v(z^d - D)$, $\ell^6(z^6) = v^6(z^6)$ and $\ell^d(z^d) = \min_{a \in A} h^d(z^d, a, \ell^{d+1})$, $d = 1, \cdots, 5$. We remark that $\ell^d(z^d)$ would be the solution to the optimality equations if the determination of the $\{a^d\}$ could take place in the morning of day d prior to the departure of the blood mobiles to their collection sites. In the following proposition, we show that the $\{\ell^d\}$ are lower bounds on the $\{v^d\}$.

Proposition 4 *The functions* $\{\ell^d\}$ *are lower bounds on the* $\{v^d\}$ *and satisfy the following inequalities:*

$$\ell^6(z^6) = v^6(z^6)$$

$$\ell^5(z^5) \leq v^5(a^5, z^5) \text{ for all } a^5,$$

$$\ell^d(z^d) \leq v^d(a^d, a^{d+1}, z^d) \text{ for all } a^d \text{ and } a^{d+1} \text{ for } d = 1, \cdots, 4.$$

Furthermore, $\ell^d(z^d)$ *is non-decreasing in* z^d *for all* $d \in \{1, \cdots, 6\}$ *if* v^6 *is non-increasing in* z^6*.*

Determination of the $\{\ell^d\}$ remains computationally demanding due to the large cardinality of the action space. Fortunately, the isotonicity of $\{\ell^d\}$ enables significant action elimination. We now present a general result of action elimination on the action space (vector space).

2.3.3 Action Elimination

Consider a finite horizon Markov decision process with $T < \infty$ decision epochs $t = 0, 1, \cdots, T-1$. Let $s(t)$ be the state of the system at epoch $t = 0, \cdots, T$, having finite state space S_t. Let $a(t)$ be the action selected at epoch $t = 0, \cdots, T-1$, having finite action space A_t. We assume that $a(t)$ is selected at epoch t, based on knowledge of $s(t)$. Let $D(t)$ be a random variable at epoch $t = 0, \cdots, T-1$. We assume the realization of $D(t)$ is a member of the finite set D_t. The realization of $D(t)$ is revealed after action $a(t)$ is selected, for all t. State process dynamics are described by $s(t+1) = f_t(s(t), a(t), d(t))$ where $d(t)$ is the realization of $D(t)$. We assume the conditional probabilities $p_t(d|s, a)$ are known for all t, where $p_t(d|s, a)$ is the probability that $D(t)$ will have realization d, given $s(t) = s$ and $a(t) = a$.

Let $c_t(s, a)$ be the (single period) cost accrued between epochs t and $t+1$, given $s(t) = s$ and $a(t) = a$. Further, let $c_T(s)$ be the terminal cost accrued at epoch T, given $s(T) = s$. Assuming the usual finite horizon, expected total cost criterion, the optimality equation is

$$v_t(s) = \min\{h_t(s, a, v_{t+1}) : a \in A_t\} \tag{6}$$

having boundary condition $v_T(s) = c_T(s)$, where $h_t(s, a, v) = c_t(s, a) + \sum_d p_t(d|s, a) * v(f_t(s, a, d))$.

We remark that if $f_t(s, a, d) = d$ for all t, then the problem formulation and the optimality equation assumes the standard form found in [60] and elsewhere. Further, it is straightforward to convert this problem and its optimality equation into the standard form found in [60] and elsewhere. However, we will find the above form of this problem description and concomitant optimality equation (6) useful. We now present a valuable action elimination result, following a preliminary definition.

Definition 1 *For all t, let A_t^{ND} be the set of all non-dominated actions in A_t, where:*

1. *Action a dominates action a' if $c_t(s, a) \leq c_t(s, a')$ for all s, and $q_t(k|s, a') \leq q_t(k|s, a)$ for all s and k, where $q_t(k|s, a) = \sum_{d \geq k} p_t(d|s, a)$, and at least one of these inequalities is a strict inequality.*

2. *Action a' is non-dominated if there exists no action a that dominates it.*

Proposition 5 *Assume:*

- *$c_t(s, a)$ is non-decreasing in s for all a.*

- *$c_T(s)$ is non-decreasing in s.*

- *$f_t(s, a, d)$ is non-decreasing in s for all a and d.*

- *$p_t(d|s,a)$ is independent of s for all a and d; i.e., $p_t(d|s,a) = p_t(d|a)$.*

Then v_t is non-decreasing for all t.

Additionally, assume:

- *$f_t(s,a,d)$ is non-increasing in d for all s and a.*

Then, search for an action in A_t that achieves the minimum in (6) can be restricted to A_t^{ND}.

Proposition 5 allows us to restrict the search of the optimal action to A_t^{ND}. Let $|B|$ be the cardinality of the set B. For the application (Chapter 4) in the thesis, the ratio $|A_t|/|A_t^{ND}|$ is approximately 10^2.

Proposition 6 *Based on above assumptions, additionally assume:*

- *There exists a real-valued function g on A_t^{ND} such that if $g(a) \leq g(a')$, then $q_t(k|a) \leq q_t(k|a')$ for all s and k.*
- *v_t is convex for all t; i.e., $v_t(s+1) - v_t(s) \geq v_t(s) - v_t(s-1)$ for all s.*

Then, there exists an optimal decision $a_t^*(s)$ such that $g(a_t^*(s))$ is non-decreasing in s.

We remark that this proposition extends the monotone policy to a vector action space, given real-valued function $g(a)$, which results in further limiting our search for an optimal decision. Note the state space S_t is still totally ordered, but the action space A_t can now also be totally ordered.

Let A^{ND} be the set of all non-dominated actions in set A. In the following corollaries, we show that in determining the lower bounds $\{\ell^d\}$, it is not necessary to search the entire action set A, and that search can be restricted to a set A^{ND}. Also it is possible to have an optimal decision rule that is non-decreasing by a scalar function (function s in Corollary 2).

Corollary 1 *For all* $d = 1, \cdots, 5$,

$$\min_{\{a \in A\}} \left\{ c^d(a,a) + \sum_D P^d(D|a)\ell^{d+1}(z-D) \right\}$$
$$= \min_{\{a' \in A^{ND}\}} \left\{ c^d(a',a') + \sum_D P^d(D|a')\ell^{d+1}(z-D) \right\}.$$

Corollary 2 *Assume that (i) ℓ^{d+1} is non-decreasing and convex and, (ii) there exists a real-valued function s on A^{ND} such that if $s(a) \leq s(a')$, then $\sum_{D \geq k} P^d(D|a) \leq \sum_{D \geq k} P^d(D|a')$ for all $k \geq 0$. Then there exists an optimal decision rule δ^d such that if $z' \leq z$", then $s(\delta^d(z')) \leq s(\delta^d(z"))$.*

We remark that determining whether or not action a' is dominated by action a requires $K+1$ comparisons, where K is the number of possible realizations of $D(a)$ and $D(a')$. Thus, although A^{ND} can be determined from A offline, determining A^{ND} can require significant computational time. Specifically, to determine A^{ND}, one needs to 1) compute $c^d(a,a)$ and $\sum_{D \geq k} P(D|a)$ for any $a \in A$ and all $0 \leq k \leq K$, and 2) for each action $a \in A$, check if it is dominated based on Definition 1. While the first step takes $O(3^N)$ computational time, the second step takes $O(3^N 3^N K)$ time.

If there exists a real-valued function s on A such that $s(a) \leq s(a')$ implies $\sum_{D \geq k} P(D|a)$ $\leq \sum_{D \geq k} P(D|a')$ for all $k \geq 0$ and hence the function s totally orders A^{ND}, then the number of comparisons for determining whether or not action a' is dominated by action a can be reduced to 2, resulting in a significant reduction in computational time.

Interestingly, statistical analyses of the data provided by ARC described in Section 4.1 indicate that such a function s exists for these data, $s(a) = E(D(a))$. The basis of this result is the following lemma.

Lemma 1 *If the following conditions hold, then* $P(Y' \geq \alpha) \geq P(Y \geq \alpha)$ *for all* $\alpha \geq 0$.

1. Y *is normally distributed with mean* μ *and standard deviation* σ
2. Y' *is normally distributed with mean* μ' *and standard deviation* σ'
3. $\sigma' \geq \sigma$
4. $\sigma'/\mu' \leq \sigma/\mu$.

As we discuss in Section 4.1, a good statistical fit of the data provided by ARC implies that $D(a)$ is normally distributed with mean $E(D(a))$ and variance $Var(D(a))$, where for all a there is a strictly positive constant τ such that $E(D(a)) = \tau Var(D(a))$. For actions a and a', associate Y with $D(a)$ and Y' with $D(a')$. It then follows that if a and a' are such that $E(D(a)) \leq E(D(a'))$, then $Var(D(a)) \leq Var(D(a'))$ and hence Assumption 3 in Lemma 1 holds. Note further that Assumption 3 and $E(D(a)) = \tau Var(D(a))$ for all a imply that Assumption 4 also holds. Thus, for the $P(D|a)$ determined in Section 4.1, $E(D(a)) \leq E(D(a'))$ implies $\sum_{D \geq k} P(D|a) \leq \sum_{D \geq k} P(D|a')$ for all $k \geq 0$. Therefore, if actions a, a' are in the non-dominated set, then $c^d(a,a) < c^d(a',a')$ implies that $\sum_{D \geq k} P(D|a) \leq \sum_{D \geq k} P(D|a')$ for all $k \geq 0$.

We remark that in our numerical studies based on the ARC data, all ℓ^d thus far generated have been convex. Furthermore, it is straightforward to determine whether or not ℓ^{d+1} is convex as it is being constructed with little additional computational overhead, and if it is convex, then we can restrict the search over the non-dominated set of actions as indicated by Proposition 6 when determining ℓ^d. The determination of conditions that guarantee ℓ^d is both non-decreasing and convex for all d, given v^6 is non-decreasing and convex, is a topic of future research.

2.3.4 A Suboptimal Design

We now discuss how to use the optimal policy from relaxation model to generate suboptimal policy of original MDP model. [6] and [7] provide a survey of suboptimal control, that generally starts with a heuristic policy and then improve it by policy iteration and get an approximation. [71] considers such an approach for a multimodule MDP, and several approximation methodologies for POMDP (partially observable Markov decision process) are presented in [70], [73], [46], and [45].

Determining the lower bounds $\{\ell^d\}$ produces the policy $\{\delta^d\}$, which is an optimal policy for the relaxation problem. We let this policy be the actual collection schedule. Next, we wish to determine a collection plan $\{a^d\}$ that satisfies the constraint $\delta^d(z^d) \leq a^d$ for all possible z^d for all d. Realizing that this collection plan must be determined at least two days in advance and that all we know about $\{z^d\}$ is that $z^d \geq z^{d+1}$ for all d, we select $a^1 = \delta^1(z^1)$, $a^2 = M\delta^2(z^1)$, $a^3 = M\delta^3(z^1)$, $a^4 = M\delta^4(z^2)$, and $a^5 = M\delta^5(z^3)$, where for $\delta^d(z) = \{(\delta_{1n}(z), \delta_{2n}(z)), n = 1, \cdots, N\}$, $M\delta^d(z) = \{(M\delta_{1n}(z), M\delta_{2n}(z)), n = 1, \cdots, N\}$ and $M\delta_{in}(z) = max\{\delta_{in}(z') : z' \leq z\}$ for $i = 1, 2$. Such a selection of $\{a^d\}$ guarantees that $\delta^d(z^d) \leq a^d$ for all d. Thus, $\{a^d, \delta^d\}$ is a feasible suboptimal design that can be used to generate an upper bound on the $\{v^d\}$, which we present in Proposition 7 as follows.

Proposition 7 *Let $u^1(z^1)$ be defined recursively as follows:*

$$\begin{aligned}
u^6(z^6) &= v^6(z^6),\\
u^5(z^3, z^5) &= c^5(M\delta^5(z^3), \delta^5(z^5)) + \sum_D P^5(D|\delta^5(z^5))u^6(z^5 - D),\\
u^4(z^2, z^3, z^4) &= c^4(M\delta^4(z^2), \delta^4(z^4)) + \sum_D P^4(D|\delta^4(z^4))u^5(z^3, z^4 - D),\\
u^3(z^1, z^2, z^3) &= c^3(M\delta^3(z^1), \delta^3(z^3)) + \sum_D P^3(D|\delta^3(z^3))u^4(z^2, z^3, z^3 - D),\\
u^2(z^1, z^2) &= c^2(M\delta^2(z^1), \delta^2(z^2)) + \sum_D P^2(D|\delta^2(z^2))u^3(z^1, z^2, z^2 - D),\\
u^1(z^1) &= c^1(\delta^1(z^1), \delta^1(z^1)) + \sum_D P^1(D|\delta^1(z^1))u^2(z^1, z^1 - D).
\end{aligned}$$

Then,

$$\begin{aligned}
u^6(z^6) &\geq v^6(z^6),\ \forall z^6 \leq z^1,\\
u^5(z^3, z^5) &\geq v^5(M\delta^5(z^3), z^5),\ \forall z^5 \leq z^3, z^3 \leq z^1\\
u^4(z^2, z^3, z^4) &\geq v^4(M\delta^4(z^2), M\delta^5(z^3), z^4),\ \forall z^4 \leq z^3, z^3 \leq z^2, z^2 \leq z^1\\
u^3(z^1, z^2, z^3) &\geq v^3(M\delta^3(z^1), M\delta^4(z^2), z^3),\ \forall z^3 \leq z^2, z^2 \leq z^1\\
u^2(z^1, z^2) &\geq v^2(M\delta^2(z^1), M\delta^3(z^1), z^2),\ \forall z^2 \leq z^1,\\
u^1(z^1) &\geq v^1(\delta^1(z^1), M\delta^2(z^1), z^1).
\end{aligned}$$

We name this procedure to find a feasible policy of the original MDP model Heuristic 1.1, and the full steps are presented as follows:

Step 1. Determine the lower bounds $\{\ell^d\}$ and the optimal policy $\{\delta^d\}$.
Step 2. Determine $\{a^d\}$ and set the collection policy as $\{a^d, \delta^d\}$.
Step 3. Evaluate the policy $\{a^d, \delta^d\}$ and calculate the upper bound $u^1(z^1)$.

Algorithm 1: Heuristic 1.1

The use of $\{\delta^d\}$ for both the upper and lower bounds and the common cost and state transition structures permit the determination of an analytic bound on $u^1(z^1)-\ell^1(z^1)$, providing an analytic measure of the sub-optimal policy $\{a^d, \delta^d\}$. We now present this bound in the following proposition.

Proposition 8 *Let*

$$
\begin{aligned}
\kappa^5(z^3, z^5) =& c^5(M\delta^5(z^3), \delta^5(z^5)) - c^5(\delta^5(z^5), \delta^5(z^5)) \\
\kappa^4(z^2, z^3, z^4) =& c^4(M\delta^4(z^2), \delta^4(z^4)) - c^4(\delta^4(z^4), \delta^4(z^4)) \\
& + \sum_D P^4(D|\delta^4(z^4))\kappa^5(z^3, z^4 - D) \\
\kappa^3(z^1, z^2, z^3) =& c^3(M\delta^3(z^1), \delta^3(z^3)) - c^3(\delta^3(z^3), \delta^3(z^3)) \\
& + \sum_D P^3(D|\delta^3(z^3))\kappa^4(z^2, z^3, z^3 - D) \\
\kappa^2(z^1, z^2) =& c^2(M\delta^2(z^1), \delta^2(z^2)) - c^2(\delta^2(z^2), \delta^2(z^2)) \\
& + \sum_D P^2(D|\delta^2(z^2))\kappa^3(z^1, z^2, z^2 - D) \\
\kappa^1(z^1) =& \sum_D P^1(D|\delta^1(z^1))\kappa^2(z^1, z^1 - D).
\end{aligned}
$$

Then,

$$
\begin{aligned}
u^5(z^3, z^5) - \ell^5(z^5) &= \kappa^5(z^3, z^5), \\
u^4(z^2, z^3, z^4) - \ell^4(z^4) &= \kappa^4(z^2, z^3, z^4), \\
u^3(z^1, z^2, z^3) - \ell^3(z^3) &= \kappa^3(z^1, z^2, z^3), \\
u^2(z^1, z^2) - \ell^2(z^2) &= \kappa^2(z^1, z^2), \\
u^1(z^1) - \ell^1(z^1) &= \kappa^1(z^1).
\end{aligned}
$$

It follows from the definition of $c^d(a^d, a)$ that $c^d(a^d, a) - c^d(a, a)$ is the number of cryo bags placed in the bloodmobiles minus the number of cryo bags actually used to collect cryo times Δ.

A generalization of Heuristic 1.1: The choice of $\{a^d\}$ for Heuristic 1.1 insures that $\{a^d, \delta^d\}$ is feasible for given $\{\delta^d\}$. This choice of $\{a^d\}$ is very conservative in that it insures there are a sufficient number of cryo bags on the mobile collection vehicles on day $d \in \{1, \cdots, 5\}$ even if no cryo units are collected in the past two days. A generalization of the choice of $\{a^d\}$ is: $a^1 = \delta^1(z^1)$, $a^2 = M\delta^2(z^1 - y^2)$,

$a^3 = M\delta^3(z^1 - y^3)$, $a^4 = M\delta^4(z^2 - y^4)$, and $a^5 = M\delta^5(z^3 - y^5)$, for $y^d \geq 0$, $d = 2, \cdots, 5$. Recalling that $z^{d+1} = z^d - D^d$, y^2 can be thought of as a surrogate for the random variable D^1 and for $d = 3, 4$, and 5, y^d can be thought of as a surrogate for $D^{d-2} + D^{d-1}$. In order to insure that the policy used is feasible for this more general choice of $\{a^d\}$, we use $\{\bar{\delta}^d\}$, where:

$$\bar{\delta}^1(z^1) = \delta^1(z^1),$$

$$\bar{\delta}^2(z) = \begin{cases} \delta^2(z) & \forall\ z \leq z^1 - y^2 \\ \delta^2(z^1 - y^2) & \forall z \geq z^1 - y^2 \end{cases}$$

$$\bar{\delta}^d(z) = \begin{cases} \delta^d(z) & \text{if } z \leq z^{d-2} - y^d, \text{ and } d \in \{3, 4, 5\} \\ \delta^d(z^{d-2} - y^d) & \text{if } z \geq z^{d-2} - y^d, \text{ and } d \in \{3, 4, 5\} \end{cases}$$

Let $\{\bar{u}^d\}$ be the expected cost generated by this more general choice of $\{a^d\}$ and $\{\bar{\delta}^d\}$, given $\{y^d\}$. The $\{\bar{u}^d\}$ then satisfy:

$$\begin{aligned}
\bar{u}^6(z^6) =& v^6(z^6), \\
\bar{u}^5(z^3, z^5, y^5) =& c^5(M\delta^5(z^3 - y^5), \bar{\delta}^5(z^5)) + \sum_D P^5(D|\bar{\delta}^5(z^5))\bar{u}^6(z^5 - D), \\
\bar{u}^4(z^2, z^3, z^4, y^4, y^5) =& c^4(M\delta^4(z^2 - y^4), \bar{\delta}^4(z^4)) \\
& + \sum_D P^4(D|\bar{\delta}^4(z^4))\bar{u}^5(z^3, z^4 - D, y^5), \\
\bar{u}^3(z^1, z^2, z^3, y^3, y^4, y^5) =& c^3(M\delta^3(z^1 - y^3), \bar{\delta}^3(z^3)) \\
& + \sum_D P^3(D|\bar{\delta}^3(z^3))\bar{u}^4(z^2, z^3, z^3 - D, y^4, y^5), \\
\bar{u}^2(z^1, z^2, y^2, y^3, y^4, y^5) =& c^2(M\delta^2(z^1 - y^2), \bar{\delta}^2(z^2)) \\
& + \sum_D P^2(D|\bar{\delta}^2(z^2))\bar{u}^3(z^1, z^2, z^2 - D, y^3, y^4, y^5), \\
\bar{u}^1(z^1, y^2, y^3, y^4, y^5) =& c^1(\delta^1(z^1), \delta^1(z^1)) \\
& + \sum_D P^1(D|\delta^1(z^1))\bar{u}^2(z^1, z^1 - D, y^2, y^3, y^4, y^5).
\end{aligned}$$

Further, let $\{y^d\}$ be such that $\bar{u}^d \leq u^d$ for all d. Then, in the following proposition, we show that Proposition 8 holds, where $\{\bar{u}^d\}$ replaces $\{u^d\}$ and the equalities are replaced by inequalities ($\leq$).

Proposition 9 *It follows that*

$$
\begin{aligned}
\bar{u}^5(z^3, z^5) - \ell^5(z^5) &\leq \kappa^5(z^3, z^5), \\
\bar{u}^4(z^2, z^3, z^4) - \ell^4(z^4) &\leq \kappa^4(z^2, z^3, z^4), \\
\bar{u}^3(z^1, z^2, z^3) - \ell^3(z^3) &\leq \kappa^3(z^1, z^2, z^3), \\
\bar{u}^2(z^1, z^2) - \ell^2(z^2) &\leq \kappa^2(z^1, z^2), \\
\bar{u}^1(z^1) - \ell^1(z^1) &\leq \kappa^1(z^1).
\end{aligned}
$$

Heuristics 1.2 and 1.3: Heuristics 1.2 and 1.3 are based on the above generalization of Heuristic 1.1 and differ only in how the $\{y^d\}$ are selected. Heuristic 1.2 assumes that $y^2 = y^3 = y^4 = y^5$ and that $\bar{u}^1(z^1, y^2, y^3, y^4, y^5)$ is minimized with respect to the scalar value $y = y^2 = y^3 = y^4 = y^5$. Heuristic 1.3 assumes the search for a minimum of $\bar{u}^1(z^1, y^2, y^3, y^4, y^5)$ is over all four variables, y^2, y^3, y^4, and y^5. We show in Section 4.2 that (1) Heuristic 1.1 produces the largest upper bound and Heuristic 1.3 produces the smallest upper bound and (2) Heuristic 1.1 requires the smallest computational time and Heuristic 1.3 requires the longest computational time. Throughout, we use linear search and local search to find a good y^d even though optimality is not guaranteed.

In the next chapter, we discuss how to evaluate the policies from Heuristic 1.1-1.3. We further develop some structural results of optimal policy under multiple penalty functions, and use them to build an algorithm to find $\delta^d(z)$ efficiently.

CHAPTER III

CHANCE CONSTRAINED MODELS AND THEIR EVALUATIONS

3.1 Introduction

In Chapter 2, we determined an actual collection schedule $\{\delta^d\}$, a feasible daily collection plan $\{a^d\}$ such that $\delta^d \leq a^d$, a lower bound $\{\ell^d\}$ and an upper bound $\{u^d\}$ on $\{v^d\}$, and a bound on the difference between the upper and lower bounds $\{\kappa^d\}$ for an MDP with terminal cost. In this chapter, we aim to compare policies on the basis of cost due to cryo bags used and mid-day pickups, which excludes any terminal cost, assuming that the risk of not achieving the weekly target for cryo production is sufficiently low. We describe this risk in terms of a chance constraint.

We consider two main approaches for policy comparison. The first approach, considered in Section 3.3, is based on the MDP model developed in Chapter 2. The first step is to adjust the terminal cost structure in order for the pair $\{\delta^d, a^d\}$ to satisfy the chance constraint. The second step is to separate the single period costs from the terminal cost, where the single period costs capture the costs of the cryo bags used and the mid-day pickup costs but exclude any terminal cost.

The second and more direct approach is to consider an MDP with a chance constraint. A critical limitation of this approach is that a standard application of DP does not reliably produce an optimal policy for multi-stage MDPs with chance constraints. Our (open-loop feedback control [8]) approach treats each multi-stage (i.e., multi-day) MDP with a chance constraint as a single-stage problem. We then examine a (simple, easy to understand and implement) heuristic associated with this second approach and compare this heuristic to the heuristics generated by the first approach.

3.2 Policy Evaluation

Determining the expected weekly cryo bag and mid-day pickup cost of the policy $\{a^d, \delta^d\}$: The cost structure of the cryo collection problem is composed of (1) a single period cost $c^d(a^d, a)$ that only considers the costs of mid-day pickups and of cryo bags used and (2) a terminal cost v^6. It is straightforward to show that the set of lower bound expected cost functions $\{\ell^d\}$ is of the form $\{\ell_1^d, \ell_2^d\}$, where $\ell_1^d(z^d) = h^d(z^d, \delta^d(z^d), \ell_1^{d+1})$, $\ell_1^6(z^6) = 0$, $\ell_2^d(z^d) = \sum_D P^d(D|\delta^d(z^d))\ell_2^{d+1}(z^d - D)$, $\ell_2^6(z^6) = v^6(z^6)$, and $\ell^d(z^d) = \ell_1^d(z^d) + \ell_2^d(z^d)$ for all d.

We remark that $\{\ell_1^d\}$ only considers the expected cost attributed to mid-day pickups and cryo bags, and $\{\ell_2^d\}$ only considers the expected cost attributed to the terminal cost. The sets $\{u^d\}$ and $\{v^d\}$ share the same structural characteristic; i.e., $\{u^d\} = \{u_1^d, u_2^d\}$ and $\{v^d\} = \{v_1^d, v_2^d\}$, where u_1^d and v_1^d only consider the expected cost attributed to mid-day pickups and cryo bags and u_2^d and v_2^d only consider the expected cost attributed to the terminal cost. It is straightforward to show that $u_2^1(z^1) = \ell_2^1(z^1)$. Hence, the expected cost is attributed to only mid-day pickups and cryo bags generated by the policy $\{a^d, \delta^d\}$, i.e., Heuristic 1.1, is $u_1^1(z^1) = u^1(z^1) - u_2^1(z^1)$.

Satisfying the chance constraint $P(z^6 \leq 0) \geq \tau$: We now present several approaches that insure that policy $\{a^d, \delta^d\}$ satisfies the constraint $P(z^6 \leq 0) \geq \tau$. We begin by determining $P(z^6 \leq 0)$, given $\{a^d, \delta^d\}$ and z^1. Let $P(D^d|z^d) = P^d(D^d|\delta^d(z^d))$. Then for $j \leq i$, $P(z^6 = j|z^5 = i) = P(D^5 = i - j|z^5 = i)$. Let $P(z^6 = j|z^{d+1} = i)$ be given for $j \leq i$. Then, we can determine $P(z^6 \leq 0|z^1)$ as follows:

$$P(z^6 = j | z^d = i) = \sum_{j \le k \le i} P(z^6 = j, z^{d+1} = k | z^d = i)$$
$$= \sum_{j \le k \le i} P(z^6 = j | z^{d+1} = k) P(D^d = i - k | z^d = i).$$

For our numerical analysis, we have considered various values of m in order to insure the constraint $P(z^6 \le 0) \ge \tau$ is satisfied.

3.3 Adjust Penalty Function to Satisfy the Chance Constraint

We considered three types of penalty functions:

1. Step function, $v^6(z) = m \cdot \mathbf{1}_{\{z>0\}}$, where $\mathbf{1}_{\{A\}}(x)$ is the indicator function, which equals 1 if $x \in A$ and 0 otherwise.

2. Linear function, $v^6(z) = m \cdot max\{z, 0\}$.

3. Quadratic function, $v^6(z) = m \cdot [max\{z, 0\}]^2$.

where m is a constant penalty coefficient.

The step function provides a penalty when the target is not achieved but does not increase as the deviation from the target increases. Thus, we have decided not to use this penalty function. The penalty coefficient m for the linear function can be interpreted as the unit cost of cryo for cryo units required to be purchased from other sources in order to meet the weekly target. However, a linear function does not capture the preference, held by members of the ARC management team, that a large target miss should be penalized significantly more than a small target miss. A quadratic function captures this preference and as a result, it is the penalty that we use. Note that all of these contenders are monotone and hence all of the structural policy results presented in Chapter 2 hold.

In the following subsections, we present additional structural policy results that can be used to improve the computational time when searching for optimal policies by varying the value of m in order to satisfy the chance constraint, assuming $v^6(z) = m \cdot [max\{z, 0\}]^2$. Once m is changed, the optimal policy $\{\delta^d\}$ may change and hence may need to be recomputed, and recomputing an optimal policy can be time-consuming. We now determine structural results that can reduce the time needed to recompute $\{\ell^d\}$ and $\{\delta^d\}$. We present one general result (Lemma 2) and two corollaries. Corollary 3 ensures that the one-stage cost ($c^d(a, a)$) of an optimal policy is monotone in m, which affects the number of elements in the action space that need to be searched as m is varied. The second result, Corollary 4, determines when an optimal policy will not need to be recomputed, given a change in m.

3.3.1 Monotone Policy under Multiple Penalty Functions

We begin this section with a lemma that gives conditions that imply the non-dominated set of actions can be totally ordered. Let $h(z, a, v) = c(a) + \sum_D P(D|a)v(z - D)$ and assume $s : A^{ND} \mapsto \mathbf{R}$ is such that $s(a) \leq s(a')$ if and only if $\sum_{D \geq k} P(D|a) \leq \sum_{D \geq k} P(D|a')$, for all k.

Lemma 2 *Let v and v' be such that if $z' \leq z$, then $v'(z') - v(z') \leq v'(z) - v(z)$. Let $\bar{a}, \bar{a}' \in A^{ND}$ be such that*

$$h(z, \bar{a}, v) \leq h(z, \bar{a}', v),$$

$$h(z, \bar{a}', v') \leq h(z, \bar{a}, v'),$$

where at least one of these inequalities is strict. Then, $c(\bar{a}) \leq c(\bar{a}')$.

Define $h^d(z, a, v) = c^d(a, a) + \sum_D P^d(D|a)v(z - D)$, and let $\ell_i^d(z) = min_a h^d(z, a, \ell_i^{d+1})$ for given ℓ_i^6. Define $\mathcal{D}_i^d(z) = argmin\ h^d(z, a, \ell_i^{d+1})$. The next result follows directly from Lemma 2.

Corollary 3 *Assume that if $z' \leq z$, then*

$$\ell_2^{d+1}(z') - \ell_1^{d+1}(z') \leq \ell_2^{d+1}(z) - \ell_1^{d+1}(z).$$

Let $a_1 \in \mathcal{D}_1^d(z)$, $a_2 \in \mathcal{D}_2^d(z)$, and $a_2 \notin \mathcal{D}_1^d(z)$ and/or $a_1 \notin \mathcal{D}_2^d(z)$. Then $c^d(a_1, a_1) \leq c^d(a_2, a_2)$.

Clearly, if $\ell_2^6 \geq \ell_1^6$, then $\ell_2^d \geq \ell_1^d$ for all d. If we assume $\ell_1^6(z) = m[max(0, z)]^2$, $\ell_2^6(z) = m'[max(0, z)]^2$, and $m < m'$, then it follows that if $z' \leq z$, then $\ell_2^6(z') - \ell_1^6(z') \leq \ell_2^6(z) - \ell_1^6(z)$.

We remark that we have not shown that (i) implies (ii), where:
(i) if $z' \leq z$, then $\ell_2^{d+1}(z') - \ell_1^{d+1}(z') \leq \ell_2^{d+1}(z) - \ell_1^{d+1}(z)$,
(ii) if $z' \leq z$, then $\ell_2^d(z') - \ell_1^d(z') \leq \ell_2^d(z) - \ell_1^d(z)$,
which is a topic for future research.

Further, we have not shown that $a_1 \notin \mathcal{D}_2^d(z)$ and/or $a_2 \notin \mathcal{D}_1^d(z)$ when $a_1 \in \mathcal{D}_1^d(z)$ and $a_2 \in \mathcal{D}_2^d(z)$. We have yet to find counter examples to these easily checked conditions. Hence, as a heuristic, we totally order A^{ND} as follows:

$$a \prec a' \text{ if and only if } c^d(a, a) \leq c^d(a', a').$$

This heuristic assumption allows us to restrict search for $\delta_2^d(z)$, given $\delta_1^d(z)$, to $\{a \in A^{ND} : c^d(a, a) \geq c^d(\delta_1^d(z), \delta_1^d(z))\}$ for the case where $\ell_1^6(z) = m[max(0, z)]^2$, $\ell_2^6(z) = m'[max(0, z)]^2$, and $m < m'$.

We note that the conclusion of Corollary 3 is not $c^d(a_2, a_2) \geq c^d(a_1, a_1)$, $\forall a_2 \in \mathcal{D}_2^d(z)$. We construct a counter example as follows. Assume $\mathcal{D}_1^d(z) = \mathcal{D}_2^d(z) = \{a, a'\}$ where $c^d(a, a) < c^d(a', a')$. If a' is chosen as the optimal action for $\ell_1^d(z)$, and a is chosen as the optimal policy for $\ell_2^d(z)$, then the monotonicity of the one-stage cost structure for an optimal policy is violated (e.g., $c^d(a', a') \leq c^d(a, a)$ is the contradiction). However, we look for an optimal action ($\delta^d(z)$) in reality, not a set of all optimal actions ($\mathcal{D}^d(z)$), therefore reducing the size of the action space (A^{ND}) by adding the constraint $c^d(a, a) \geq c^d(a_1, a_1)$ does not affect the optimality of the problem.

3.3.2 A Robust Policy under Multiple Penalty Functions

Corollary 3 presents conditions that imply $c^d(\delta_1^d(z), \delta_1^d(z)) \leq c^d(\delta_2^d(z), \delta_2^d(z))$, so if an optimal action under one penalty function ($\delta_1^d(z)$) is known, an optimal action associated with another penalty function ($\delta_2^d(z)$) can be obtained by searching a subset of A^{ND}. We now present conditions that insure an action remains optimal over an interval of values of m.

Corollary 4 *Let $\ell^d(z, m) = min_a h^d(z, a, \ell^{d+1}(\cdot, m))$, where $\ell^6(z, m) = m[max(0, z)]^2$, and define $\mathcal{D}^d(z, m) = argmin\ h^d(z, a, \ell^{d+1}(\cdot, m))$. Assume $m' < m''$ and $m \in [m', m'']$. If $z' \leq z$, then the following inequalities hold:*

$$\ell^{d+1}(z', m'') - \ell^{d+1}(z', m) \leq \ell^{d+1}(z, m'') - \ell^{d+1}(z, m),$$
$$\ell^{d+1}(z', m) - \ell^{d+1}(z', m') \leq \ell^{d+1}(z, m) - \ell^{d+1}(z, m').$$

Further, assume $a' \in \mathcal{D}^d(z, m'') \cap \mathcal{D}^d(z, m')$. Then, $a' \in \mathcal{D}^d(z, m)$.

Thus, under the assumptions presented in Corollary 4, if a' is a member of $\mathcal{D}^d(z, m'')$ and $\mathcal{D}^d(z, m')$ and $m \in [m', m'']$, then a' is a member of $\mathcal{D}^d(z, m)$ and hence there is no need to search for an optimal action for any $m \in [m', m'']$.

Based on the above results and assuming the conditions in Corollaries 3 and 4 hold for all d, we now present Algorithm 2, where $v^6(z) = m * [max\{z, 0\}]^2$:

> **Step 0.** Let $m_{min} < m_{max}$ and $step > 0$. Set $n = 1$. Determine an optimal policy $\{\delta_1^d\}$ and calculate $P_1 = P(z^6 \leq 0)$, given penalty parameter m_{min}. Assume $P_1 < \tau$; otherwise, readjust m_{min} (decrease m_{min}). Determine an optimal policy $\{\delta_{max}^d\}$ and calculate $P_{max} = P(z^6 \leq 0)$, given penalty parameter m_{max}. Assume $P_{max} \geq \tau$; otherwise, readjust m_{max} (increase m_{max}).
>
> **Step 1.** Let $m_{n+1} = m_n + step$, determine an optimal policy $\{\delta_{n+1}^d\}$ and calculate $P_{n+1} = P(z^6 \leq 0)$, given penalty parameter m_{n+1}. Use Corollaries 3 and 4 to reduce the search over all actions in order to determine $\{\delta_{n+1}^d\}$, given $\{\delta_n^d\}$ and $\{\delta_{max}^d\}$.
>
> **Step 2.** If $P_{n+1} \geq \tau$, then terminate with solution $\{\delta_{n+1}^d\}$. Otherwise, let $n = n + 1$ and go to Step 1.

Algorithm 2: Adjust m to find optimal policy $\delta^d(z)$

Throughout, we assume $P(z^6 \leq 0)$ is increasing in m and that as m increases, so does $c^d(\delta^d(z), \delta^d(z))$ for all d and z. The first assumption, albeit as yet unproven, is based on the intuition that the probability of meeting the target should increase as the penalty function increases, and this assumption is justified by our numerical results. The second assumption is proved by Corollary 3, and guarantees that given an optimal policy $\{\delta^d\}$ for m, if we seek an optimal policy for $m' > m$, then the action a such that $c^d(a, a) < c(\delta^d(z), \delta^d(z))$ for given d and z need not be considered. Algorithm 2 given above increases m in increments of $step$ until m is large enough to satisfy the chance constraint, taking advantage of this fact. Algorithm 1 is a finite algorithm that is not intended to find the smallest value of m that satisfies the chance constraint but will return a value of m that satisfies the chance constraint within $step$ of this minimum value. For our application, we found good parameter choices were $m_{min} = 1, m_{max} = 10$, and $step = 2$.

3.4 MDP with a Chance Constraint

Thus far, we have adjusted a parameter in the penalty function of the MDP with a terminal cost in order to (indirectly) insure that the chance constraint is satisfied. In this section, we take a more direct approach. In particular, we remove the penalty function and examine the MDP with a chance constraint. Use of dynamic programming for a multi-period MDP with a chance constraint may lead to a sub-optimal policy, which we show by an example. To avoid this possibility, on day d, we will determine the actual collection schedule for day d, $d+1$, $\cdots$, 5 (Friday) as a single period problem, knowing only z^d, and then apply the actual collection schedule determined for day d. Once z^{d+1} becomes available, we will again determine the actual collection schedule for day $d+1$, $d+2$, $\cdots$, 5 (Friday) as a single period problem, knowing only z^{d+1}, and then apply the actual collection schedule determined for day $d+1$. Such an approach is sometimes referred to as an "open loop feedback" control policy, which is sub-optimal (but often quite good) to the usual closed-loop feedback control policy of the MDP.

3.4.1 Literature Review on Chance Constrained MDPs

Derman and Klein [24] first introduced the constrained Markov decision process and proposed linear programming based solutions. Sample path constrained MDPs were studied by Ross and Varadarajan [61], which were shown to satisfy Bellman's principle of optimality by Haviv [37]. However, Haviv [37] pointed out that the principle of optimality is violated in multi-stage Markov decision processes with constraints on the expected state-action frequencies, thus significantly limiting the computational tractability of the problem formulation.

Stewart and White [67, 72] used heuristics to determine optimal solutions in a multi-objective problem. Delage et al.[20] presented a chance-constrained formulation for MDPs with uncertain parameters and showed that in some instances second-order cone programming can solve this problem efficiently. Blackmore et al. [10] used chance constraints to ensure the probability of failure is below a given threshold, presented an approximate method to solve the chance-constrained stochastic control problem, and showed that the problem can be solved by mixed-integer programming techniques. Borkar et al. [12] modeled risk by a measure called conditional Value-at-Risk and proposed an iterative offline algorithm for finding a risk-constrained optimal policy. Shapiro [65] discussed the concept of time consistency of multistage risk averse stochastic programming problems and showed some approaches were not time consistent. Ruszczynski [62] introduced a Markov risk measure to formulate risk-averse control problems where risk-averse dynamic programming equations are derived.

In the context of the cryo collection problem, we address this violation of the principle of optimality as follows. We model the cryo collection problem as a chance constrained MDP by removing the terminal cost and adding a chance constraint. We present a counterexample to show that DP cannot be used to determine an optimal policy for the chance constrained MDP. Next, we treat the chance constrained MDP as a single stage optimization problem, determining all decisions from the current day through the remainder of the week. We show that this problem is equivalent to an integer program (IP) under some conditions and calculate an optimal decision rule using an IP solver. Once the collection yield for the day is known and the number of units of cryo needed to satisfy the weekly target has been updated, we again use this IP, properly modified to consider one less day, to determine an optimal decision rule for the remainder of the week. We follow this open-loop feedback procedure throughout the rest of the week.

We also introduce a simple, easy implemented greedy algorithm, Heuristic 2.1, to solve the problem. Heuristic 2.1 is also an open-loop feedback procedure. We use both the chance constrained IP method and the Heuristics 1.1 through 1.3 as benchmarks for Heuristic 2.1. We remark that the Heuristics 1.1 through 1.3 require adjustment for proper comparison since the Heuristics 1.1-1.3 are based on a terminal cost structure, rather than a chance constaint.

3.4.2 A Counter Example

A counter example to the statement that DP determines an optimal solution to an MDP with a chance constraint is first presented by Haviv [37]. However, Haviv constructs an infeasible state ("chain 1" in [37], where a state is *feasible* if there exists a policy, when applied from this state, that can satisfy the chance constraint) in his counter example. In this section, we present a counter example in the context of the cryo collection problem to show that even when all states are *feasible* (i.e., the chance constraint is satisfied), the use of dynamic programming may not result in an optimal policy.

Let $\tau = 0.95$, i.e., the tolerance of not meeting the target is 5% and hence we need to ensure we achieve the target by the end of the week with at least 95%. Suppose on Thursday, there is only one policy a^4 that generates 60 units with probability (in short, w.p.) 0.2, 50 units w.p. 0.8; On Friday, there are two policies a_1^5 and a_2^5, where a_1^5 generates 70 units w.p. 0.9, 50 units w.p. 0.04, 40 units w.p. 0.03, 30 units w.p.

0.03; a_2^5 generates 70 units w.p. 0.93, 50 units w.p. 0.06, 30 units w.p. 0.01. Costs of a^4, a_1^5 and a_2^5 are \$1, \$1 and \$2, respectively. See Figure 1 for probability distributions.

$$a^4 = \begin{cases} 60\ w.p.\ 0.2 \\ 50\ w.p.\ 0.8 \end{cases}, \quad a_1^5 = \begin{cases} 70\ w.p.\ 0.9 \\ 50\ w.p.\ 0.04 \\ 40\ w.p.\ 0.03 \\ 30\ w.p.\ 0.03 \end{cases}, \quad a_2^5 = \begin{cases} 70\ w.p.\ 0.93 \\ 50\ w.p.\ 0.06 \\ 30\ w.p.\ 0.01 \end{cases}$$

Figure 1: Summary of distributions

Let the balance on Thursday $z^4 = 100$, and since there is only one policy a^4, the possible balances on Friday are 40 and 50. It can be shown that the optimal policy on Friday is $\delta^5(40) = a_1^5$, $\delta^5(50) = a_2^5$. On Thursday, there are four policies in terms of Friday's balance z^5 - (a_1^5, a_1^5), (a_1^5, a_2^5), (a_2^5, a_1^5), (a_2^5, a_2^5), where (a_1^5, a_2^5) means choose a_1^5 when $z^5 = 40$ and choose a_2^5 when $z^5 = 50$. Note the policy on Thursday is always a^4, so it is ignored here. See Table 1 for the four policies on Thursday.

Table 1: Four policies on Thursday when $z^4 = 100$

4 Policies	$\delta^4(100)$	$\delta^5(40)$	$\delta^5(50)$	Expected Cost	Prob. of Missing Target
$\{a^4, (a_1^5, a_1^5)\}$	a^4	a_1^5	a_1^5	\$2	0.054
$\{a^4, (a_1^5, a_2^5)\}$	a^4	a_1^5	a_2^5	\$2.8	0.014
$\{a^4, (a_2^5, a_1^5)\}$	a^4	a_2^5	a_1^5	\$2.2	0.05
$\{a^4, (a_2^5, a_2^5)\}$	a^4	a_2^5	a_2^5	\$3	0.01

The first policy (a_1^5, a_1^5) is not feasible (the chance constraint is not satisfied), while the other three policies satisfy the chance constraint. (a_2^5, a_1^5) has the smallest cost on Friday (\$1.2), so on Thursday, the optimal policy should be (a_2^5, a_1^5). However, this violates the optimality on Friday. See Table 2 for the optimal policy on Friday. Note that while all states are feasible in this example, an optimal policy is not determined using backward dynamic programming. See Figure 2 for illustration.

Table 2: Optimal policy on Friday

z^5	$\delta^5(z^5)$	Expected Cost	Prob. of Missing Target
40	a_1^5	\$1	0.03
50	a_2^5	\$2	0.01

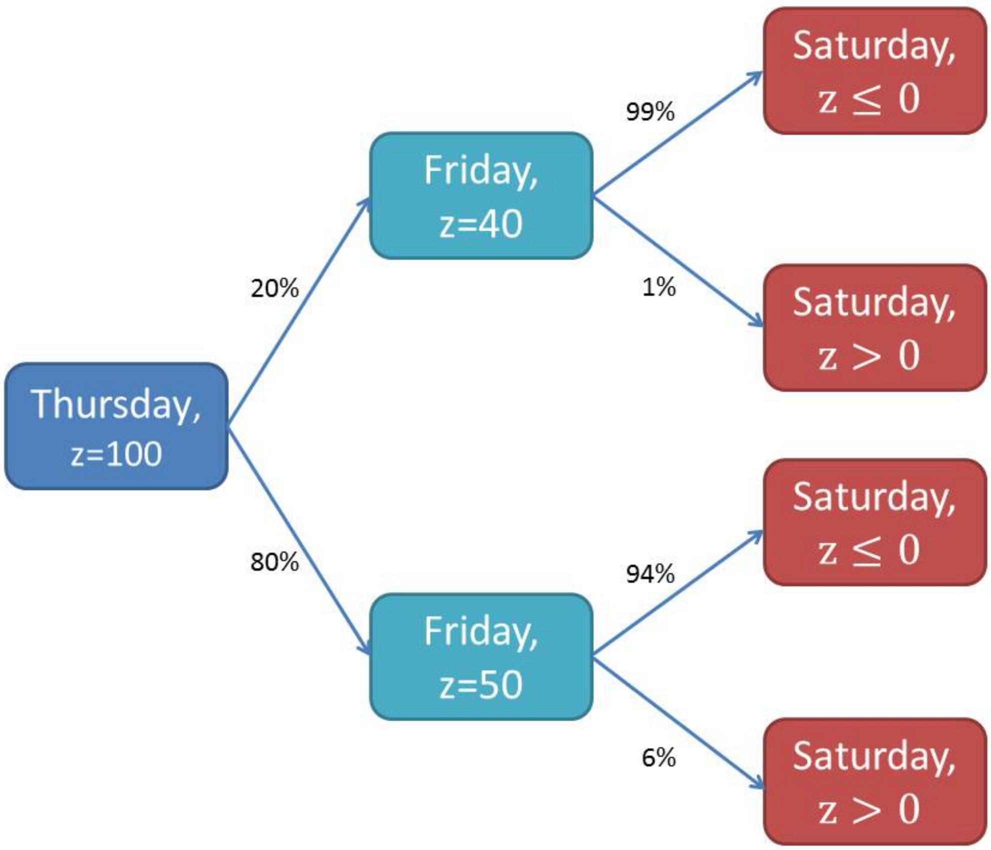


Figure 2: Optimal policy on Thursday when $z^4 = 100$

3.4.3 A Chance-Constrained MDP Model

We construct the chance constrained MDP model as follows.

Time horizon: Let $d = 1, \cdots, 5$ represent the five days of the week from Monday ($d = 1$) to Friday ($d = 5$) for cryo collection.

State space: For $d = 1$, the state space is $S = \{z^1\}$, and for $d = 2, 3, 4$, the state space is $S = \{a^d, a^{d+1}, z^d\}$, where a^d, a^{d+1} represent the daily collection plans for day d and $d+1$, and z^d represents the left weekly target from day d onwards. For $d = 5$, the state space is $S = \{a^5, z^5\}$. Note the state space is the same as the state space of the MDP model with a terminal cost.

Action: For any state on day d, we determine the actual collection schedule and (when applicable) the daily collection plan for day $d+2$, and also the actual collection schedule for all possible states for all days $d' > d$ throughout the remainder of the week and (when applicable) the daily collection plan for day $d' + 2$. The actual collection schedule for day d and day $d + 1$ are constrained by the daily collection plans for day d and day $d + 1$. We denote this decision rule by π^d. In comparison, given the same state, we determine only the actual collection schedule for day d and (when applicable) the daily collection plan for day $d + 2$ (a^{d+2}) for the MDP having a terminal cost. We remark that the decision determined for day d includes not only a for day d and (when applicable) a^{d+2} for day $d + 2$, but also the decision rules for all following days since dynamic programming does not ensure an optimal policy for the chance constrained MDP. We now explicitly state the action for each day:

1. On Friday ($d = 5$), we determine the actual collection schedule a subject to $a \leq a^5$. The action is $\pi^5(a^5, z^5) = a$.

2. On Thursday ($d = 4$), we determine the actual collection schedule a subject to $a \leq a^4$ and the decision rule on Friday for any possible state (a^5 with any z such that $z \leq z^4$). The action is $\pi^4(a^4, a^5, z^4) = \{a, \{\pi^5(a^5, z), \forall z \leq z^4\}\}$.

3. On Wendesday ($d = 3$), we determine the daily collection plan for Friday (a^5), the actual collection schedule $a \leq a^3$, and the decision rule on Thursday for any possible state (a^4, a^5 with any z such that $z \leq z^3$). The action is $\pi^3(a^3, a^4, z^3) =$

$\{a, a^5, \{\pi^4(a^4, a^5, z), \forall z \leq z^3\}\}$.

4. On Tuesday ($d = 2$), we determine the daily collection plan for Thursday (a^4), the actual collection schedule $a \leq a^2$, and the decision rule on Wednesday for any possible state (a^3, a^4 with any z such that $z \leq z^2$). The action is $\pi^2(a^2, a^3, z^2) = \{a, a^4, \{\pi^3(a^3, a^4, z), \forall z \leq z^2\}\}$.

5. On Monday ($d = 1$), we determine the daily collection plans for Monday, Tuesday and Wednesday (a^1, a^2 and a^3), and the decision rule on Tuesday for any possible state (a^2, a^3 with any z such that $z \leq z^1$). The action is $\pi^1(z^1) = \{a^1, a^2, a^3, \{\pi^2(a^2, a^3, z), \forall z \leq z^1\}\}$.

Dynamics: Let D^d, a random variable, be the number of cryo units collected on day d. The probability distribution of D^d depends on the actual collection schedule a on day d. For $d = 1, \cdots, 5$, $z^{d+1} = z^d - D^d$. Let P^d be the transition probability from day d to day $d + 1$, defined in the same way as in Chapter 2.

Cost structure: Let $c^d(a^d, a)$ be the one-stage cost, which includes the mid-day pickup cost and the additional cost for cryo bags on day d. Note that $c^d(a^d, a)$ is the same one-stage cost defined in Chapter 2.

Objective and the chance constraint: We minimize the total expected cost to achieve the weekly target with probability no less than τ (e.g. $\tau = 0.95$), i.e., $P(z^6 \leq 0) \geq 0.95$.

Given a decision rule π^d, let v^d be the total expected cost function from day d throughout the remainder of the week. Then,

$$
\begin{aligned}
v^1(z^1, \pi^1(z^1)) =& c^1(a^1, a^1) + \sum P^1(D|a^1)* \\
& v^2(a^2, a^3, z^1 - D, \pi^2(a^2, a^3, z^1 - D)) \\
v^2(a^2, a^3, z^2, \pi^2(a^2, a^3, z^2)) =& c^2(a^2, a) + \sum P^2(D|a)* \\
& v^3(a^3, a^4, z^2 - D, \pi^3(a^3, a^4, z^2 - D)) \\
v^3(a^3, a^4, z^3, \pi^3(a^3, a^4, z^3)) =& c^3(a^3, a) + \sum P^3(D|a)* \\
& v^4(a^4, a^5, z^3 - D, \pi^4(a^4, a^5, z^3 - D)) \\
v^4(a^4, a^5, z^4, \pi^4(a^4, a^5, z^4)) =& c^4(a^4, a) + \sum P^4(D|a) v^5(a^5, z^4 - D, \pi^5(a^5, z^4 - D)) \\
v^5(a^5, z^5, \pi^5(a^5, z^5)) =& c^5(a^5, a).
\end{aligned}
$$

Let V^d be the optimal total expected cost function from day d throughout the remainder of the week. Then,

$$
\begin{aligned}
V^1(z^1) &= min_{\{\pi^1(z^1)\}}\left\{ v^1(z^1, \pi^1(z^1)) \right\} && s.t. P(z^6 \leq 0) \geq \tau \\
V^2(a^2, a^3, z^2) &= min_{\{\pi^2(a^2,a^3,z^2)\}}\left\{ v^2(a^2, a^3, z^2, \pi^2(a^2, a^3, z^2)) \right\} && s.t. P(z^6 \leq 0) \geq \tau \\
V^3(a^3, a^4, z^3) &= min_{\{\pi^3(a^3,a^4,z^3))\}}\left\{ v^3(a^3, a^4, z^3, \pi^3(a^3, a^4, z^3)) \right\} && s.t. P(z^6 \leq 0) \geq \tau \\
V^4(a^4, a^5, z^4) &= min_{\{\pi^4(a^4,a^5,z^4)\}}\left\{ v^4(a^4, a^5, z^4, \pi^4(a^4, a^5, z^4)) \right\} && s.t. P(z^6 \leq 0) \geq \tau \\
V^5(a^5, z^5) &= min_{\{\pi^5(a^5,z^5)\}}\left\{ v^5(a^5, z^5, \pi^5(a^5, z^5)) \right\} && s.t. P(z^6 \leq 0) \geq \tau
\end{aligned}
$$

A state is said to be *feasible* if and only if there is a policy such that the chance constraint can be satisfied when the policy is applied from this state. For example, if the state is (a^d, a^{d+1}, z^d), then this state is feasible if there is a policy π such that $P(z^6 \leq 0|\pi, a^d, a^{d+1}, z^d) \geq \tau$. Therefore, $P(z^6 \leq 0) \geq \tau$ is satisfied for all feasible states, and we obtain the optimal policy at these feasible states by the above equations. However, if a state is infeasible, we apply the policy that collects as much blood as possible for cryo. The optimal cost (V^d) for an infeasible state is the corresponding expected cost based on this policy. For infeasible states, this policy reflects the decision to maximize the total number of blood units collected for cryo regardless of cost if we are not able to achieve the weekly target.

Relaxation model: Similar to Chapter 2, if the daily collection plan can be determined at the beginning of the day, rather than two days in advance, then the daily collection plan and the actual collection schedule become identical, the state becomes $S = \{z^d\}$, and a policy on day d depends only on z^d. Hence, the cardinalities of the state and action spaces and the search for an optimal policy are greatly reduced. The relaxation model is presented as follows.

Given a decision rule π^d, let l^d be the total expected cost function based on the state and action from day d through the remainder of the week. Then,

$$
\begin{aligned}
l^1(z^1, \pi^1(z^1)) &= c^1(a^1, a^1) + \sum P^1(D|a^1) l^2(z^1 - D, \pi^2(z^1 - D)) \\
l^2(z^2, \pi^2(z^2)) &= c^2(a^2, a^2) + \sum P^2(D|a^2) l^3(z^2 - D, \pi^3(z^2 - D)) \\
l^3(z^3, \pi^3(z^3)) &= c^3(a^3, a^3) + \sum P^3(D|a^3) l^4(z^3 - D, \pi^4(z^3 - D)) \\
l^4(z^4, \pi^4(z^4)) &= c^4(a^4, a^4) + \sum P^4(D|a^4) l^5(z^4 - D, \pi^5(z^4 - D)) \\
l^5(z^5, \pi^5(z^5)) &= c^5(a^5, a^5).
\end{aligned}
$$

Define L^d be the optimal total expected cost function based on the state from day d

through the remainder of the week. Then,

$$L^1(z^1) = min_{\{\pi^1(z^1)\}}\left\{l^1(z^1, \pi^1(z^1))\right\} \qquad s.t. P(z^6 \leq 0) \geq \tau$$

$$L^2(z^2) = min_{\{\pi^2(z^2)\}}\left\{l^2(z^2, \pi^2(z^2))\right\} \qquad s.t. P(z^6 \leq 0) \geq \tau$$

$$L^3(z^3) = min_{\{\pi^3(z^3)\}}\left\{l^3(z^3, \pi^3(z^3))\right\} \qquad s.t. P(z^6 \leq 0) \geq \tau$$

$$L^4(z^4) = min_{\{\pi^4(z^4)\}}\left\{l^4(z^4, \pi^4(z^4))\right\} \qquad s.t. P(z^6 \leq 0) \geq \tau$$

$$L^5(z^5) = min_{\{\pi^5(z^5)\}}\left\{l^5(z^5, \pi^5(z^5))\right\} \qquad s.t. P(z^6 \leq 0) \geq \tau$$

The relaxation model removes the constraint $a \leq a^d$ of the original model, and thus the optimal value of the relaxation model provides a lower bound for the optimal value of the original model, i.e., $L^d \leq V^d$.

Computational intractability: Since the procedure for determining an action for day d for the chance constrained MDP involves determining actions for day d throughout the remainder of the week, the cardinality of the number of actions to be searched grows exponentially as d gets smaller. Consider the relaxation model for example, if $N = 10$ every day, the weekly target is 1000, and there are 3 actions for any site, then the action space cardinality on Monday is $3^{10}(10^3 3^{10})^4 = O(10^{35})$. Note that computationally this represents a significantly more challenging problem than the MDP relaxation model with a terminal cost, which would have an action space with cardinality $3^{10} = O(10^4)$.

3.4.4 One-stage Chance Constrained Problem

We now consider a one-stage chance constrained optimization problem where all daily collection plans are made in the beginning of the week and there are no need to adjust them and determine the actual daily collections later in the week.

Decision: A (weekly) decision a is a sequence of actions, e.g., $\{a^1, a^2, a^3, a^4, a^5\}$, where a^d is the actual collection schedule on day d. For simplicity, let $a = \{(a_{1n}, a_{2n}), n = 1, \cdots, N\}$, where N is the number of sites of the week, $a_{ij} = 1(0)$ means assigning a cryo (non-cryo) collection for the i-th interval of j-th site.

Dynamics: $P(D|a)$ is the probability of collecting D blood units given the weekly decision a. $z^6 = z^1 - D$.

Cost structure: Let $c^d(a^d, a^d)$ be the one-stage cost including additional (expected) cryo bag cost and mid-day pickup cost, then the total cost is $c(a, a) = \sum_{d=1}^{5} c^d(a^d, a^d)$.

Objective and the chance constraint: We want to minimize the total cost and ensure that the weekly target is achieved with probability no less than τ (e.g. $\tau = 0.95$), i.e.,

$$Min \sum_{d=1}^{5} c^d(a^d, a^d)$$
$$s.t.\ P(z^6 \leq 0) \geq \tau$$

Computational Tractability & Analytical Results: For the one-stage chance constrainted problem, there is only one (weekly) decision to make (e.g., $a = \{a^1, a^2, a^3, a^4, a^5\}$). Let the action space A be the set of the decisions. Similar to Chapter 2, we can define the non-dominated set A^{ND} for the one stage (e.g., the entire week) as follows:

Definition 2 *Let A^{ND} be the set of all non-dominated actions in A, where:*

1. *Action a dominates action a' if $c(a, a) \leq c(a', a')$, and $\sum_{D \geq k} P(D|a) \leq \sum_{D \geq k} P(D|a')$ for all k, and at least one of these inequalities is a strict inequality..*

2. *Action a' is non-dominated if there exists no action a that dominates it.*

By Definition 2, we have a similar action elimination result:

Proposition 10 *There exists an optimal action in the set A^{ND}, where A^{ND} is the set of non-dominated actions for the one-stage chance constrained problem.*

Proposition 10 implies that we can restrict the search for an optimal policy to the actions in the non-dominated set. However, constructing the non-dominated set can be quite difficult for a large N. Note N is the number of sites for the entire week and if we only consider three actions for a site, then the size of the action space is 3^N. For example, based on the real data from the ARC, the maximum number of sites per week during the four weeks in March 2012 is 57. Then the size of the action space for such a week is 3^{57} which is $O(10^{27})$. Therefore, constructing A^{ND} becomes intractible.

We now show that we can transform the split version of this model to an IP and use currently available IP solvers to solve the IP to the optimality, thus producing a good sub-optimal policy for the cryo problem. We remark that we need the assumption that the number of units of blood collected follows a Normal distribution based on the projected number of units of blood to be collected, an assumption that is validated in Section 4.1.

Given $2N$ collection intervals for the entire week, let $p = \{p_i\}$ be the vector of the number of units of blood projected to be collected, $c = \{c_i\}$ be the vector of the transport costs and $a = \{a_i\}$ be the binary vector of decision variables, where $i = 1, \cdots, 2N$. That is, p_i, c_i and a_i are the projected blood collection amount, the transport cost and the decision variable of whether to designate a cryo collection for the i-th interval, respectively. Note that if i is the first interval of a collection window, then c_i is the mid-day pickup cost of the corresponding site, and if i is the second interval, then $c_i = 0$. The total projected amount of cryo collection is $p^T a$, and the total transport (mid-day pickup) cost is $c^T a$.

Proposition 11 *Assume that the number of units of blood collected is Normally distributed based on the projected number of units of blood to be collected, i.e.,* $D \sim N(\mu p^T a, \sigma^2 p^T a)$. *Then the chance constraint* $P(z^6 > 0) \le \alpha$ *is equivalent to the linear constraint* $p^T a \ge (\frac{z_\alpha \sigma + \sqrt{(z_\alpha \sigma)^2 + 4\mu(z^d - 0.5)}}{2\mu})^2$.

For example, if $z^1 = 1000$ and the maximum of the probability of missing the target is 0.05, then $z_{0.05} = 1.645$ and the constraint is $p^T a \ge 2362.2$.

By Proposition 11, the chance constraint can be transformed to a linear constraint. We remark that the objective function of the one-stage chance constrained problem is also linear, i.e., $u\mu p^T a + c^T a$, where u is the cost difference between a cryo bag and a non-cryo bag, and $\mu p^T a$ is the expected cryo collection amount, which is equal to the expected cryo bag usage. Then the one-stage chance constrained problem becomes an IP:

$$\begin{aligned} &Min\ u\mu p^T a + c^T a \\ &s.t.\ p^T a \ge (\frac{z_\alpha \sigma + \sqrt{(z_\alpha \sigma)^2 + 4\mu(z^d - 0.5)}}{2\mu})^2 \\ &a \in \{0,1\}^{2N} \end{aligned}$$

This integer program has $2N$ binary variables and one constraint, and we denote it by IP1.0. Given the size of N ($N \le 100$), the optimal solution can be easily obtained by an IP solver, e.g., CPLEX. The following proposition indicates the optimal cost is monotonically nonincreasing as α increases.

Proposition 12 *The optimal cost of IP1.0 is monotonically nonincreasing in* α.

We now can solve the one-stage chance constrained problem to optimality using an IP solver. Note, however, that the multi-stage problem quickly becomes computationally challenging. For example, if we consider a two-stage problem (Monday and the rest of the week), then given the daily collection plan (a^1) on Monday, the chance constraint becomes

$$P(z^6 > 0|a^1) = \sum_{D \in \mathcal{D}} P^1(D^1 = D|a^1) P(D^2 + D^3 + D^4 + D^5 < z^1 - D) \leq \alpha,$$

where the random variable D^d is the number of units of blood collected on day d. Note this constraint is not a linear constraint under the Normal distribution assumption, therefore solving the multi-stage problem by the above IP approach would be still computationally very expensive. In this thesis, we use a rolling horizion procedure to solve the multi-stage problem. Next, we use the policy derived from the IP to find a sub-optimal policy for the multi-stage problem by using a rolling horizon procedure.

3.4.5 Rolling Horizon Decision Making

We now present three heuristics, IP1.1, IP1.2, and Heuristic 2.1. We describe IP1.1 and IP1.2 as follows. For day d and given z^d, all current and future actions are determined by the one-stage chance constrained problem and the current actions are applied. Once z^{d+1} becomes known, all current and future actions are re-determined by the one-stage chance constrained problem from day $d+1$ onwards and the current actions are applied. This process continues until the one-stage problem on $d = 5$ (Friday) is solved and the appropriate action is taken. The third heuristic, Heuristic 2.1, uses an intuitive, easy-to-implement idea to produce actions.

IP-based Heuristic - IP1.1: Given that an optimal policy for the one-stage problem can be easily obtained, we now apply it to each stage to construct a rolling horizon procedure. We call this procedure IP1.1, the full steps of which are presented in Algorithm 3 as follows:

We remark that from Tuesday to Thursday, additional constraints $a \leq a^d$ and

Step 1. Run the one-stage stochastic optimization for the whole week, and obtain a^1, a^2, a^3.
Step 2. Given any possible z^2, run the one-stage stochastic optimization from Tuesday onwards, and obtain $a \le a^2$ and a^4.
Step 3. Given any possible z^3 and a^4, run the one-stage stochastic optimization from Wednesday onwards, and obtain $a \le a^3$ and a^5.
Step 4. Given any possible z^4, a^4 and a^5, run the one-stage stochastic optimization from Thursday onwards, and obtain $a \le a^4$.
Step 5. Given any possible z^5 and a^5, run the one-stage stochastic optimization for Friday, and obtain $a \le a^5$.
Algorithm 3: IP-based Heuristic - IP1.1

$a \le a^{d+1}$ are added to the IP since a^d and a^{d+1} have been predetermined. For Friday, the additional constraint $a \le a^5$ is added to the IP. If the problem is infeasible at one state, i.e., if the chance constraint cannot be satisfied for any policy, then we let the optimal action be "collect all blood for cryo".

Policy Evaluation: Let U^d and P^d be the cost-to-go function and the probability of missing the weekly target on day d based on the policy determined by Algorithm 3. Let $P^6(z^6) = 1$ if $z^6 \le 0$, and $P^6(z^6) = 0$ if $z^6 > 0$. Then the policy obtained from the IP1.1 can be evaluated by the following recursive equations (DP approach):

- On Friday, for all possible $\{a^5, z^5\}$ pairs, use the policy $\{a : a \le a^5\}$ to compute the values as follows,

$$U^5(a^5, z^5) = c^5(a^5, a),$$
$$P^5(a^5, z^5) = \sum_{z^6} P^6(z^6) P(z^5 - z^6 | a).$$

- On Thursday, for all possible $\{a^4, a^5, z^4\}$ pairs, use the policy $\{a : a \le a^4\}$ to compute the values as follows,

$$U^4(a^4, a^5, z^4) = c^4(a^4, a) + \sum_{D<z^4} P(D|a)U^5(a^5, z^4 - D),$$

$$P^4(a^4, a^5, z^4) = \sum_{z^5} P^5(a^5, z^5)P(z^4 - z^5|a).$$

- On Wednesday, note that a^3 is already known, for all possible $\{a^4, z^3\}$ pairs, use the policy $\{a, a^5 : a \leq a^3\}$ to compute the values as follows,

$$U^3(a^4, z^3) = c^3(a^3, a) + \sum_{D<z^3} P(D|a)U^4(a^4, a^5, z^3 - D),$$

$$P^3(a^4, z^3) = \sum_{z^4} P^4(a^4, a^5, z^4)P(z^3 - z^4|a).$$

- On Tuesday, note that a^2 is already known, for all possible z^2's, use the policy $\{a, a^4 : a \leq a^2\}$ to compute the values as follows,

$$U^2(z^2) = c^2(a^2, a) + \sum_{D<z^2} P(D|a)U^3(a^4, z^2 - D),$$

$$P^2(z^2) = \sum_{z^3} P^3(a^4, a^3)P(z^2 - z^3|a).$$

- On Monday, compute the values as follows,

$$U^1 = c^1(a^1, a^1) + \sum_{D<z^1} P(D|a^1)U^2(z^1 - D),$$

$$P^1 = \sum_{z^2} P^2(z^2)P(z^1 - z^2|a^1).$$

where $P(z^5 - z^6|a)$, $P(z^4 - z^5|a)$, $P(z^3 - z^4|a)$, $P(z^2 - z^3|a)$ and $P(z^1 - z^2|a^1)$ is the transition probability $P^d(D|a)$ in Section 2.2, all implicitly assume using the policy obtained from IP1.1. Then U^1 is the total expected cost and P^1 is the probability of missing the weekly target.

Improved IP-based Heuristic - IP1.2: We remark that IP1.1 directly applies IP1.0 at each stage by assuming the problem from that stage throughout the end of the week is a one-stage stochastic optimization problem. However, the numerical results in Chapter 4 show that IP1.1 requires substantial computational time and does not provide a good sub-optimal policy compared to Heuristic 1.1-1.3. This is because:

1. IP1.1 generates many different daily collection plans for Thursday and Friday due to different values of z^2 and z^3. As a result, there are many IPs to solve in order to generate the policy for the entire week, requiring significant computational time.

2. An optimal action for the one-stage problem is very sensitive to z^d. For example, if the actual blood collection amount on Monday is greater than expected, the one-stage optimal policy from Tuesday onwards will have fewer cryo collection intervals, regardless of the possibility of less cryo collection later in the week. Similarly, if the actual blood collection amount on Monday is less than expected, the one-stage optimal policy from Tuesday onwards will have more cryo collection intervals, regardless of the cost of a mid-day pickup. The result is a poor balance between minimizing cost (especially the mid-day pickup cost) and achieving the weekly cryo collection target.

We now present two ways to reduce the computational time and improve the heuristic performance:

1. Only consider the mid-day pickup cost in the objective function and ignore the cost difference between the cryo bag and the non-cryo bag.

2. Determine the actual collection schedule a and the daily collection plan a^{d+2} conservatively by adding constraints that do not cancel any end-of-day deliveries

for the current day and plan all end-of-day deliveries for day $d+2$, i.e., $a \geq min\{a^d, \{(0,1), \cdots, (0,1)\}\}$, $a^{d+2} \geq \{(0,1), \cdots, (0,1)\}$.

The intent of the first method is to reduce the number of daily collection plans on Thursday and Friday by ignoring the additional bag cost of a cryo bag, relative to the cost of a non-cryo bag. This method is reasonable since this difference of cost is minimal. The second method is to use all end-of-day deliveries regardless of the chance constraint. This method is also reasonable because (1) the end-of-day delivery has no extra transport cost and hence the additional total cost is only slightly increased, and (2) it minimizes the number of mid-day pickups that are needed.

For example, if the remaining balance is z^2 on Tuesday, the integer program is:

$$\begin{aligned}
&Min\ c^T a \\
&\ \ s.t.\ p^T a \geq LB(z^2) \\
&\qquad a_{\{1:2(N_2+N_3)\}} \geq min\{\{a^2, a^3\}, \{(0,1), \cdots, (0,1)\}\} \\
&\qquad a_{\{2(N_2+N_3)+1:2(N_2+N_3+N_4)\}} \geq \{(0,1), \cdots, (0,1)\} \\
&\qquad a \in \{0,1\}^{2(N-N_1)}
\end{aligned}$$

where $LB(z^2)$ is the lower bound on projected collections given by Proposition 11, $a_{\{1:2(N_2+N_3)\}}$ is the actual collection schedule on Tuesday and the actual collection schedule on Wednesday, and $a_{\{2(N_2+N_3)+1:2(N_2+N_3+N_4)\}}$ is the daily collection plan on Thursday. N_d is the number of sites on day d. We denote this improved heuristic by IP1.2.

IP Composition: The integer program in our problem can be solved quickly by an IP solver, e.g., CPLEX. However, even for IP1.2, there is a large number of subproblems (IPs) to solve, due to different values for z^d from Tuesday to Friday and different daily collection plans a^4 and a^5. Fortunately, all the subproblems of a day are independent, so we can combine them into a large IP and determine the optimal solutions simultaneously. In our problem, numerical results indicate that solving the large IP takes approximately the same amount of time as solving a small IP for IP1.2. Thus, we can use the IP composition instead of sequentially solving all subproblems in order to improve the total computational time, making IP1.2 competitive as a heuristic.

A Simple Heuristic - Heuristic 2.1: We now present another rolling horizon approach for determining a good sub-optimal policy. Heuristic 2.1 differs fundamentally from Heuristic 1.1 and its derivatives by assuming no terminal cost and explicitly considering the chance constraint $P(z^6 \leq 0) \geq \tau$. Heuristic 2.1 differs from IP1.1 and IP1.2 by using an intuitive and easily computed ratio. Heuristic 2.1 is a greedy heuristic that focuses on minimizing the expected cost of mid-day transportation per unit of whole blood collected for cryo. For the split case, let the random variable Y_{ind} be the number of units collected during interval $i \in \{1, 2\}$, at site n, on day d, and assume that Y_{ind} is normally distributed with mean μ_{ind} and standard deviation σ_{ind}. Let C_{ind} be the cost of a pickup for interval i, at site n, on day d. Consistent with the cost structure for Heuristic 1.1 and its derivatives, let $C_{2nd} = 0$ and assume that C_{1nd} is the cost of a mid-day pickup at site n on day d. Let $\varphi_{ind} = C_{ind}/\mu_{ind}$, the expected cost of transport per unit of whole blood collected for cryo. Heuristic 2.1 designates intervals as cryo intervals on the basis of this ratio, preferring intervals with lower ratios to intervals with higher ratios, and includes intervals until the chance constraint is achieved. Necessarily, $\varphi_{2nd} = 0$ for all n and d; thus, Heuristic 2.1 will designate all second intervals as cryo intervals before designating a first interval as a cryo interval. Note Heuristic 2.1 for non-split case ranks collection windows instead of collection intervals, and then φ is always positive. We now consider a key result for Heuristic

2.1.

Lemma 3 *Let $\{Y_j, j = 1, \cdots, J\}$ be a set of independent random variables, where X_j is normally distributed with mean μ_j and standard deviation σ_j. Let τ and $y(\tau)$ be such that $P(Z \leq y(\tau)) \geq \tau$ for the standard normal random variable Z. Assume $z \leq \sum_{j=1}^{J} \mu_j - y(\tau)\sqrt{\sum_{j=1}^{J} \sigma_j^2}$. Then, $P(z \leq \sum_{j=1}^{J} Y_j) \geq \tau$.*

J^1 can be determined as follows. Let $y(\tau)$ be such that $P(Z \leq y(\tau)) \geq \tau$ for given τ, where Z is $N(0,1)$. Choose J^1 to be the smallest integer such that $z^1 \leq \sum_{j=1}^{J^1} \mu_j - y(\tau)\sqrt{\sum_{j=1}^{J^1} \sigma_j^2}$. Then, by Lemma 3, $P(z^1 \leq \sum_{j=1}^{J^1} Y_j) \geq \tau$. We now summarize this heuristic below in Algorithm 4.

Preliminary steps:

a. Let $y(\tau)$ be such that $P(Z \leq y(\tau)) \geq \tau$ for given τ, where Z is $N(0,1)$.

b. Create the weekly list $\{\mu_j, \sigma_j, \varphi_j\}$, which is totally ordered by $\{\varphi_j\}$.

c. Set $d = 1$.

Step 1. Given z^d, choose J to be the smallest integer such that $z^d \leq \sum_{j=1}^{J} \mu_j - y(\tau)\sqrt{\sum_{j=1}^{J} \sigma_j^2}$.

Step 2. Given J, determine a^d, a^{d+1}, and a^{d+2}, as necessary.

Step 3. Let $z^{d+1} = z^d - D^d$. If $d + 1 = 6$, then stop. Otherwise, set $d = d + 1$ and revise the weekly list by removing intervals that are out-dated or prohibited by the $\{a^d\}$. Then go to Step 1.

Algorithm 4: Heuristic 2.1

To compare with IP1.0, we let Heuristic 2.0 be the open-loop algorithm that generates the policy of entire week by Heuristic 2.1 only in the beginning of week and do not adjust it later. Note Heuristic 2.0 is not guaranteed to be optimal for the one-stage problem.

3.4.6 Evaluate the Performance of IP1.1, IP1.2 and Heuristic 2.1

We consider two benchmarks for IP1.1, IP1.2, and Heuristic 2.1 to evaluate the performance:

1. Use the one-stage stochastic optimization (IP1.0). The optimal cost generated from the one-stage problem can be used as an upper bound.

2. Use the Heuristics 1.1-1.3 and the lower and upper bounds developed in Chapter 2.

Comparing Heuristics 1.1-1.3, and Heuristic 2.1: Heuristic 2.1 was developed due to its intuitive appeal and ease of implementation; however, we initially did not know the quality of the resulting sub-optimal policy. Heuristics 1.1-1.3 were developed based on principles of stochastic optimization, and we have been able to determine analytically the quality of the resulting sub-optimal policy. We now use the bounds determined for Heuristic 1.1 in order to understand the quality of the sub-optimal policy produced by Heuristic 2.1. In order to do so, two preliminary adjustments are required. The first of these adjustments removes the expected terminal cost from the total expected cost accrued by the policy $\{a^d, \delta^d\}$ determined by Heuristic 1.1, leaving only the expected extra cryo bag and mid-day pickup costs accrued through the week. The second adjustment involves adjusting the terminal cost associated with Heuristic 1.1 in order to insure that Heuristic 1.1 satisfies the chance constraint associated with Heuristic 2.1.

Comparing Heuristics IP 1.1-1.2, and Heuristic 2.1: Heuristic 2.1 and IP1.1-1.2 are rolling horizon decision-making algorithms that explicitly consider the chance constraint. The open loop feedback algorithms IP1.1 and IP1.2 were developed to improve the performance of the one-stage chance constrained problem. We use the optimal cost of the one-stage stochastic optimization problem and IP1.1-1.2 to generate upper bounds in order to quantify the quality of the sub-optimal policy created by Heuristic 2.1. Unlike Heuristic 1.1-1.3, which produce both lower and upper bounds, IP1.1-1.2 can only generate upper bounds for the MDP with a chance constraint.

We will conduct a comprehensive numerical analyses in Chapter 4 to show the parameter estimation, computation improvement, and heuristic performance.

CHAPTER IV

A CASE STUDY

In this Chapter, we implement all algorithms developed in Chapter 2 and Chapter 3 and present a comprehensive numerical analysis. We first analyze the data and estimate the parameters of the probability distribution in Section 4.1. We then present computational analyses in Section 4.2, including the analysis of action elimination, non-dominated set construction, and numerical results for Heuristic 1.1-1.3, IP1.0-1.2, and Heuristic 2.0-2.1. We describe a decision support tool in Section 4.3 that is based on Heuristic 2.1. Finally, we compare the non-split case with the split case on the basis of Heuristic 1.1-1.3 and Heuristic 2.1, and calculate the cost savings of the split case, relative to the non-split case in Section 4.4.

4.1 Data Analysis and Parameter Estimation

For estimating the model parameters, we have used real data from the ARC Southern region from 01/01/2010 to 05/10/2012, including 4993 collections from more than 3000 unique collection sites. For each collection site, the data included the date of the collection, collection site information including name and address, projected amount of collection, the beginning and ending times of the collection window, actual amount of collection, and mid-day transport cost per site based on the zip code set by the courier. The projected amount of collection was forecasted based on the number of scheduled donors and prior years' collection results for each specific site and adjusted to account for several factors, including the day of the week (e.g., Monday vs. Friday), seasonality (e.g., summer vs. fall, holiday vs. no holiday etc.), geographical location, and the time of day of the collection window (e.g., morning vs. afternoon).

To predict the actual collection given the projected amount of collection per site, we

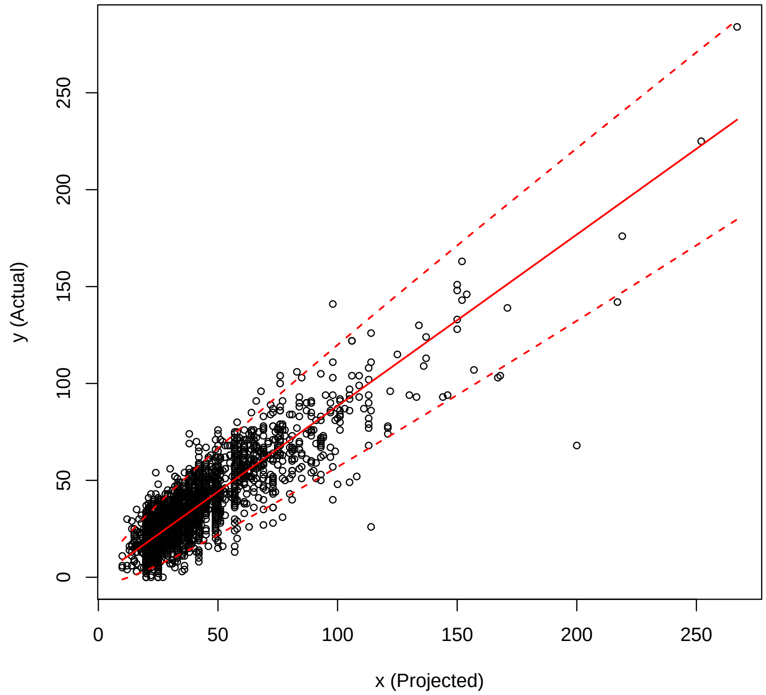


Figure 3: Prediction (solid line) and 95% prediction intervals (dashed lines) for Model 2.

considered three models based on inputs from the ARC team. In particular, letting x be the projected number of cryo units collected at a given site and the random variable Y be the actual number of units collected, we considered the following models: (1) $y \sim N(\beta x, \sigma^2)$, (2) $y \sim N(\beta x, \sigma^2 x)$, and (3) $y \sim N(\beta x, \sigma^2 x^2)$.

Note that the log-likelihood for the data after the continuity correction can be computed as

$$\log L = \sum_i \left\{ \Phi(\frac{y_i + .5 - \beta x_i}{\sigma x_i^\alpha}) - \Phi(\frac{y_i - .5 - \beta x_i}{\sigma x_i^\alpha}) \right\},$$

where $\alpha = 0,\ 0.5,$ and 1 for Models 1, 2, and 3, respectively and $\Phi(\cdot)$ is the standard normal distribution function. Using the estimates

$$\hat{\beta} = \frac{\sum_i x_i^{1-2\alpha} y_i}{\sum_i x_i^{2-2\alpha}} \quad \text{and} \quad \hat{\sigma}^2 = \frac{1}{n} \sum_i \frac{(y_i - \beta x_i)^2}{x_i^{2\alpha}},$$

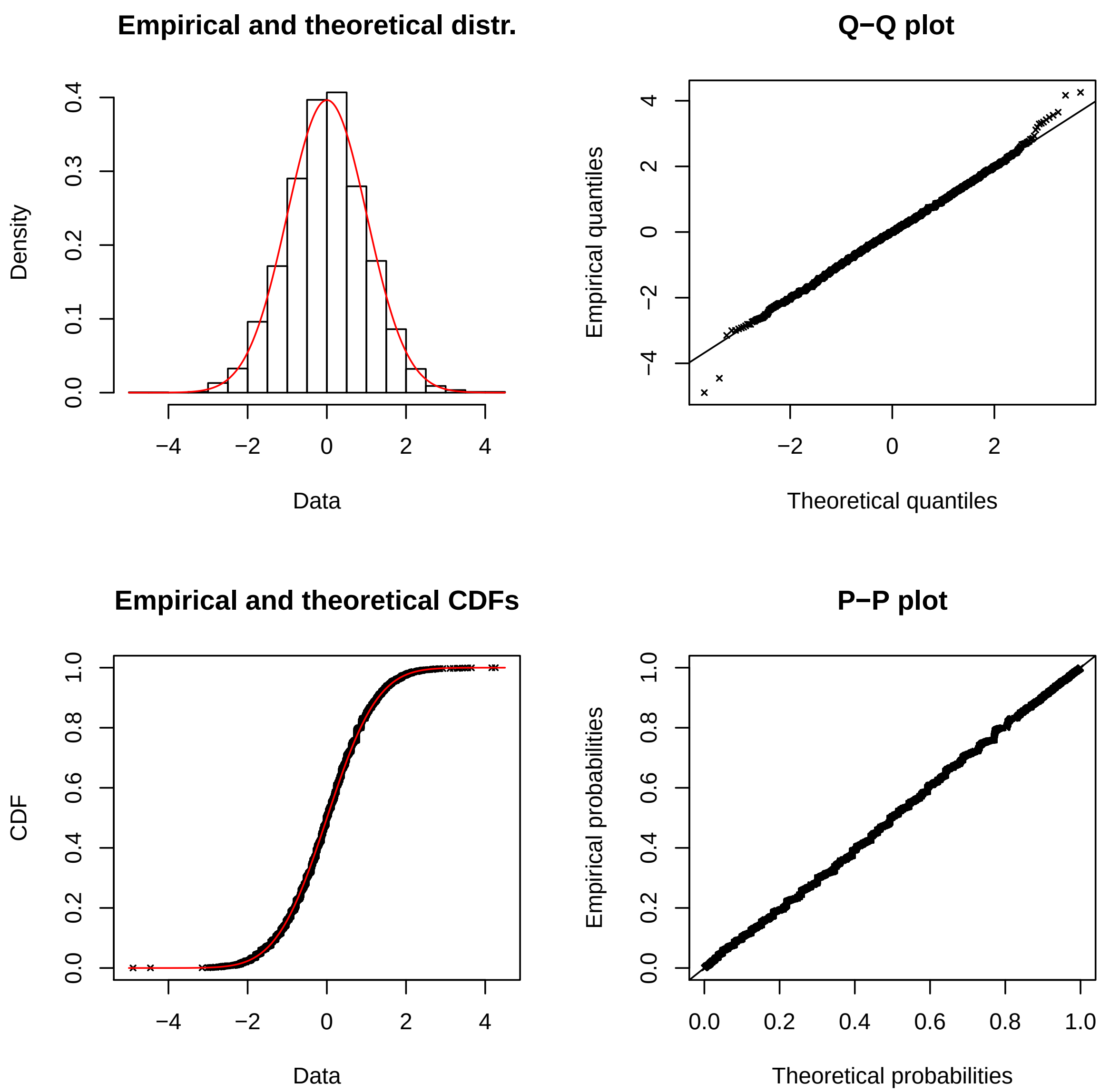


Figure 4: Checking the normality assumption of Model 2.

we obtain $\log L_1 = -14613$, $\log L_2 = -14253$, and $\log L_3 = -14361$. Since Model 2 maximizes the likelihood, it gives the best fit to the data among the three models. Interestingly, Model 2 makes also physical sense because blood collection is an additive process and hence the variances are expected to add up linearly (assuming the collections at nonoverlapping intervals to be independent). The fitted model and its 95% prediction intervals are shown in Figure 3. The normal distribution assumption can be checked using the scaled residuals: $e = (y - \beta x)/(\sigma\sqrt{x})$. The plots given in Figure 4 show that standard normal distribution provides an excellent fit for the scaled residuals.

Using Model 2, the conditional probability $P^d(D|a)$ can be computed as follows. For site n, recall that the random variables Y_{1n} and Y_{2n} are the number of units collected before and after, respectively, the mid-day departure time and that $\lambda_n \in [0,1]$ is the fraction of the collection window available for a mid-day pickup at collection site n. Then, the projected collection for the first interval at site n is $\lambda_n x_n$, where x_n is the projected number of cryo units collected at site n. Thus, under Model 2, $Y_{1n} \sim N(\beta\lambda_n x_n, \sigma^2\lambda_n x_n)$ and $Y_{2n} \sim N(\beta(1-\lambda_n)x_n, \sigma^2(1-\lambda_n)x_n)$, and for actual collection schedule $a = \{a'_{1n}, a'_{2n}\}$ on day d, the actual number of units collected for cryo is the random variable $D^d = \sum_n (Y_{1n}a'_{1n} + Y_{2n}a'_{2n})$. Assuming Y_{1n} and Y_{2n} are independent, we obtain the mean and variance of D^d, $E(D^d) = \beta \sum_n (\lambda_n a'_{1n} + (1-\lambda_n)a'_{2n})x_n$ and $Var(D^d) = \sigma^2 \sum_n (\lambda_n a'_{1n} + (1-\lambda_n)a'_{2n})x_n$. We obtain the parameters $\beta = 0.93$ and $\sigma = 1.75$ based on the data from ARC.

Since the sum of normal random variables is also normal, we obtain $D^d \sim N(E(D^d), Var(D^d))$. Finally, discretizing the normal distribution and employing a continuity correction, we obtain:

$$P(D^d = D|a) = \Phi(\frac{D + .5 - E(D^d)}{\sqrt{Var(D^d)}}) - \Phi(\frac{D - .5 - E(D^d)}{\sqrt{Var(D^d)}}).$$

4.2 Computational Analyses

In this section, we computationally analyze the results presented in Chapter 2 and Chapter 3. All numerical analyses use data provided by ARC, and results are compared against actual policies for the four weeks in March 2012, which was representative of typical ARC collections in a given year. For all of the computational results, we insure that the constraint $P(z^6 \leq 0) \geq \tau$ is satisfied and assume that $\tau = 0.95$

(a probability agreed upon by ARC management) and $z^1 = 1,000$ (the actual weekly target for the four weeks in March 2012). All computations are obtained from a server computer with 2 quad core Intel Xeon CPUs running at 2.27 GHz and uses 48GB of RAM.

We begin by examining the computational implications of reducing the action space in order to determine $\{\ell^d\}$, given Corollary 1. Second, we show that Lemma 1 and the assumption of Normal distribution can be utilized to construct the non-dominated set A^{ND} efficiently. Third, we assess the quality of the upper and lower bounds derived in Chapter 2 for the proposed heuristics (Heuristic 1.1-1.3). Fourth, for split case, we show the result of finding the sub-optimal policy by adjusting m, and using the structural policy developed in Section 3.3 to improve the computational time, and then evaluate the policy, and compare Heuristic 1.1 through Heuristic 1.3 with respect to the total expected cost, $P(z^6 > 0)$, and computational time. Fifth, for split case, we compare the performance of IP1.0 with Heuristic 2.0 for the one-stage stochastic optimization problem with a chance constraint. Sixth, for split case, we show the numerical results of IP1.1, IP1.2 and Heuristic 2.1. Lastly, we provide a comprehensive comparison for all heuristics in split case, and conclude that we should implement Heuristic 2.1 in practice.

4.2.1 Action Elimination

We now present $|A^{ND}|/|A|$ for March 2012 data in Table 3. The data presented in Table 3 indicate that $|A^{ND}|/|A|$ varies from 0.0503 to 0.0001. The ratio is especially small for realistically sized problems ($N \geq 10$), and this reduction in action space cardinality significantly improves the tractability of determining the $\{\ell^d\}$, which improves the computational performance of Heuristics 1.1-1.3.

Table 3: Impact of action elimination

	Monday		Tuesday		Wednesday		Thursday		Friday	
	ratio	N	ratio	N	ratio	N	ratio	N	ratio	N
Week 1	0.06%	12	0.19%	11	0.46%	10	0.03%	13	3.80%	7
Week 2	5.03%	7	0.09%	12	0.23%	11	0.70%	10	3.43%	8
Week 3	1.98%	5	0.82%	10	0.09%	12	0.08%	12	1.33%	9
Week 4	0.02%	13	0.01%	14	0.08%	12	0.64%	10	1.92%	8

Note. ratio: $|A^{ND}|/|A|$, i.e., proportion of the cardinalities for the set of non-dominated actions. N: number of sites.

4.2.2 Construction of A^{ND}

We now present a comparison of computational time to construct A^{ND} for March 2012 data by the definition of non-dominated set (Definition 1) and by Lemma 1. We remark that the algorithm by the definition needs lots of computation due to the condition $\sum_{D\geq k} P(D|a) \leq \sum_{D\geq k} P(D|a')$ for any k. However, Lemma 1 can simplify this condition to $E(D(a)) \leq E(D(a'))$ with the assumption of Normal distribution (validated in Section 4.1). Table 4 shows that the algorithm by Lemma 1 can construct A^{ND} much faster than the algorithm by the definition. We also remark that although A^{ND} can be determined from action space A off-line, the algorithm that requires not significant computational time is still preferred, especially when A^{ND} need to be computed online (e.g. A^{ND} need to be re-computed by varying m in Section 3.3).

From Table 4, the computational time of the algorithm by Lemma 1, T2 is much less than T1, the computational time of the algorithm by the definition. On average, T2 is only 0.3% of T1. In fact, the advantage of computing non-dominated set by Lemma 1 becomes significant as N increases. Therefore, Lemma 1 ensures that A^{ND} can

Table 4: Comparison of computational times to construct non-dominated set for the four weeks

Monday			Tuesday			Wednesday			Thursday			Friday		
T1	T2	N	T1	T2	N	T1	T2	N	T1	T2	N	T1	T2	N
184	0.5	12	77	0.2	11	26	0.1	10	507	1.5	13	0.8	0.03	7
1	0.04	7	210	0.5	12	77	0.2	11	30	0.1	10	3	0.04	8
0.6	0.02	5	25	0.1	10	230	0.5	12	202	0.5	12	8	0.03	9
575	1	13	1464	4	14	159	0.4	12	17	0.06	10	2	0.01	8

Note. T1 is the time by definition, T2 is the time by Lemma 1. The time unit is second. N: number of sites

be determined by an online algorithm, which is useful when finding the sub-optimal policy by adjusting the penalty function. We now turn our attention to the heuristics that utilize the results of Proposition 7 and offer tractable results.

4.2.3 Bounds Quality for the Proposed Heuristics

In this section, we compare the upper and lower bound values for Heuristics 1.1-1.3 as described in Propositions 8 and 9. Let $m = 10$, that is $v^6(z) = 10z^2$ if $z > 0$. Recall that Proposition 8 presents an analytical description of $u^1(z^1) - \ell^1(z^1)$, which by Proposition 9 is an upper bound on $\bar{u}^1(z^1) - \ell^1(z^1)$. Note the upper and lower bound includes the penalty function. Tables 5 and 6 provide the percentage gap between the upper and lower bounds, i.e. $(\bar{u}^1(z^1) - \ell^1(z^1))/\ell^1(z^1)$, for Heuristics 1.1–1.3 for the non-split and split cases respectively.

Table 5: The percentage gaps between the upper and lower bound, i.e. $(\bar{u}^1(z^1) - \ell^1(z^1))/\ell^1(z^1)$: non-split case

Week	$\ell^1(z^1)$	Heuristic 1.1	Heuristic 1.2	Heuristic 1.3
1	2008.8	2.69%	1.30%	1.30%
2	1748.9	2.51%	1.24%	1.14%
3	2093.0	2.20%	1.20%	1.08%
4	1923.1	2.32%	1.51%	1.32%

The results presented in Tables 5 and 6 indicate that the percentage gap between the upper and lower bound is less than 3% (non-split) and 11% (split) for Heuristics

Table 6: The percentage gaps between the upper and lower bound, i.e. $(\bar{u}^1(z^1) - \ell^1(z^1))/\ell^1(z^1)$: split case

Week	$\ell^1(z^1)$	Heuristic 1.1	Heuristic 1.2	Heuristic 1.3
1	705.46	8.18%	3.10%	2.78%
2	606.61	9.06%	3.76%	3.27%
3	826.04	5.61%	2.72%	2.48%
4	551.41	10.08%	5.03%	4.57%

1.1-1.3, which indicate the quality of these heuristics. Note the percentage gap in non-split case is smaller is due to large value of $\ell^1(z^1)$ (the denominator). Among these three heuristics, Heuristic 1.3 provides the highest quality suboptimal policy with respect to the difference between the upper and lower bound on the optimal value function, $v^1(z^1)$. On the other hand, Heuristic 1.3 is also computationally the most intensive one, as we describe in the following section. Furthermore, these results also provide benchmark statistics to assess the quality of expected cost $u_1^1(z^1)$ or $\bar{u}_1^1(z^1)$, that we use to evaluate the policy in Chapter 3.

In the following section, we numerically compare Heuristic 1.1-1.3 under different penalty functions and show how adjusting penalty parameter m changes the expected cost and probability of missing target.

4.2.4 Heuristic 1.1-1.3 as a Function of m

As noted earlier in Section 3.3, we have considered various values of m in order to insure the constraint $P(z^6 \leq 0) \geq \tau$ is satisfied. Table 7 presents the expected (additional cryo bag and mid-day pickup) cost $\bar{u}_1^1(z^1, y^2, y^3, y^4, y^5)$ and $P(z^6 \geq 0)$ for various values of m for Heuristic 1.1 (i.e., for the case where $y^d = 0$ for all d) for the split case. We note that $\bar{u}_1^1$ does not include the penalty function. Table 8 and 9 present the results for Heuristic 1.2 and Heuristic 1.3. Algorithm 2 is used to improve the computational time of finding $\{\delta^d\}$ for each m. We remark that the chosen m

is not guaranteed to be the best parameter, because Algorithm 2 only does a simple search on m.

Table 7: Expected total costs and probability of missing the weekly target for various values of m in Heuristic 1.1 for split case

	m=10		m=5		m=3		m=1	
week	Cost	P	Cost	P	Cost	P	Cost	P
1	\$734.10	1.52%	\$709.17	2.81%	**\$691.16**	**4.44%**	\$642.08	11.32%
2	\$635.04	1.27%	\$613.71	2.37%	**\$597.68**	**3.59%**	\$561.52	8.83%
3	\$834.67	1.95%	**\$807.46**	**3.49%**	\$786.69	5.33%	\$735.77	12.88%
4	\$586.37	1.79%	\$571.30	3.22%	**\$557.22**	**4.91%**	\$529.63	11.83%

Note. $P : P(z^6 > 0)$. Bold values are the best expected cost and probability of missing target.

Table 8: Expected total costs and probability of missing the weekly target for various values of m in Heuristic 1.2 for split case

	m=10		m=5		m=3		m=1	
week	Cost	P	Cost	P	Cost	P	Cost	P
1	\$693.82	1.61%	\$670.06	2.94%	**\$649.62**	**4.67%**	\$604.04	11.70%
2	\$598.66	1.34%	\$578.67	2.45%	**\$564.58**	**3.66%**	\$521.61	9.89%
3	\$807.42	2.00%	**\$777.93**	**3.60%**	\$756.32	5.45%	\$704.43	13.20%
4	\$556.02	1.84%	**\$540.00**	**3.30%**	\$522.94	5.18%	\$493.28	12.20%

Note. $P : P(z^6 > 0)$. Bold values are the best expected cost and probability of missing target.

Table 9: Expected total costs and probability of missing the weekly target for various values of m in Heuristic 1.3 for split case

	m=10		m=5		m=3		m=1	
week	Cost	P	Cost	P	Cost	P	Cost	P
1	\$692.85	1.59%	\$668.28	2.94%	**\$649.13**	**4.61%**	\$600.47	11.70%
2	\$596.97	1.32%	\$575.31	2.47%	**\$559.52**	**3.74%**	\$522.02	9.77%
3	\$806.08	1.99%	**\$777.55**	**3.57%**	\$755.77	5.44%	\$703.15	13.20%
4	\$554.08	1.83%	**\$537.69**	**3.31%**	\$522.86	5.05%	\$492.29	12.20%

Note. $P : P(z^6 > 0)$. Bold values are the best expected cost and probability of missing target.

The computational time of Heuristic 1.1 for a given m is very short and about 30 seconds. However, for Heuristic 1.2 and 1.3, the computational time is about 2 hours and 5 hours respectively for a given m, so it becomes intractible if we want to search from multiple values of m to find the minimum $\bar{u}_1^1$ and satisfy the chance constraint. We now use figures to show that the structural policy in Section 3.3 can be utilized to find the optimal action of the relaxation model under different penalty functions efficiently, and thus it can improve the computational time for Heuristic 1.2 and 1.3 for varied values of m.

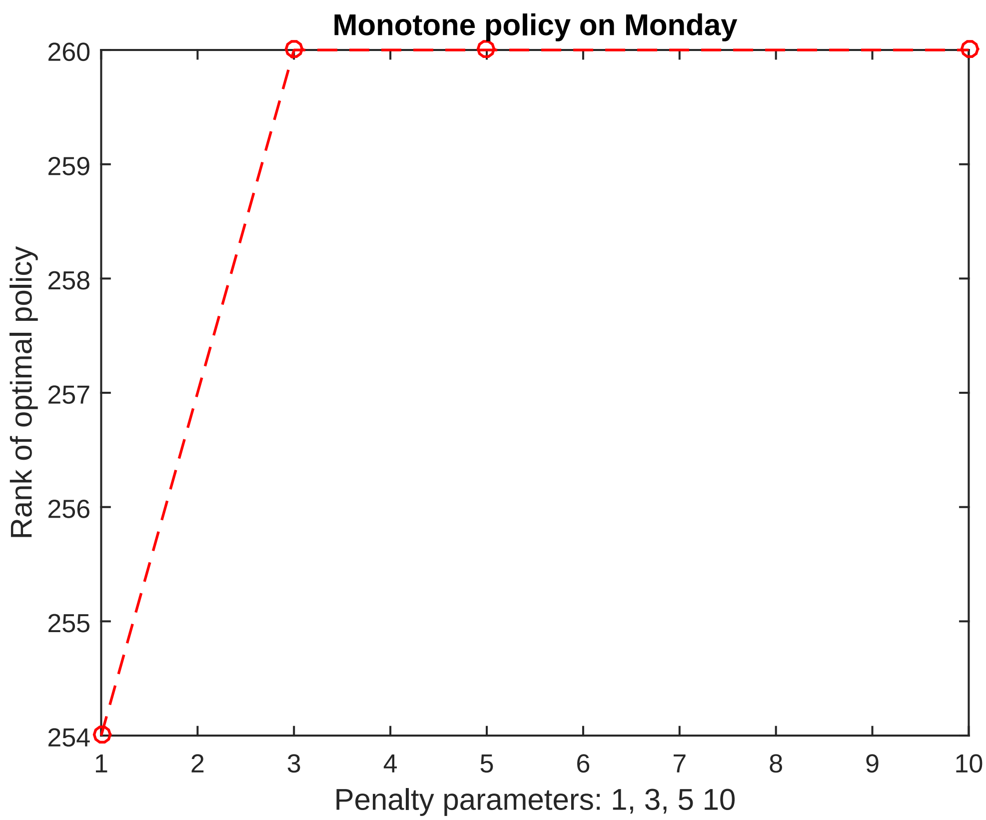


Figure 5: Actions on Monday

Figure 5 shows the optimal actions on Monday ($\delta^1(z^1)$) of the first week in March 2012, for $m = 1, 3, 5, 10$, where X-axis is the value of m, Y-axis is the rank of the action in A^{ND}, and the red circle denotes the rank of the optimal action. We note that the actions are ordered by either the one-stage cost $c^d(a, a)$ or the expected yield

$E(D|a)$, and the definition of non-dominated set and Lemma 1 ensures that the rank by $c^d(a, a)$ and the rank by $E(D|a)$ are equivalent. From Figure 5, once the optimal action of $m = 1$ is obtained, and the conditions in Corollary 3 hold, we can search optimal action for $m > 1$ from the set of non-dominated actions (A^{ND}) that the rank is not below 254. Once the optimal action of $m = 10$ is obtained, and the conditions in Corollary 3 hold, we can search the optimal action for $1 \leq m \leq 10$ from the set of non-dominated actions (A^{ND}) that the rank is between 254 and 260. Furthermore, once the optimal action of $m = 3$ is obtained, and the conditions in Corollary 4 hold, we can conclude that the optimal action for any $m \in [3, 10]$ is the action with the rank 260 (same as the optimal action for $m = 3$ or 10). Therefore, monotone policy and robust policy can be utilized to reduce the action space, and then improve the computational time of finding $\delta^d(z)$ for multiple penalty functions. Our numerical results show that the average computational time of Heuristic 1.1-1.3 can be reduced to nearly half by Algorithm 2 using this structural policy.

Figure 6, 7, 8 and 9 show the rank of the optimal action for any z^d from Tuesday to Friday of that week, for $m = 1, 3, 5, 10$. We remark that these figures along with Figure 5 validate three types of structural policy:

- Proposition 6. From Tuesday to Friday, the rank of optimal action for any m and d increases as z^d increases, and then stays same for a while, where the optimal action is the action that uses all end-of-day deliveries, and then the rank continues increasing stepwise until it reaches the highest value, and stays there afterwards, where the optimal action is the action that collects all blood for cryo.

- Corollary 3. For all d and z^d, the rank of optimal action for a small m is no larger than the rank of optimal action for a large m, and this is also intuitive, that as the penalty function increases, the decision becomes more conservative and so the one-stage cost or the expected yield increases.

- Corollary 4. The robust policy exists for different values of m. For example, for considered values of m, the region of z^d for the robust action $a = \{(0,1), \cdots, (0,1)\}$ (collect cryo by all end-of-day deliveries) is approximately $[200, 780]$ on Tuesday, $[180, 500]$ on Wednesday, $[180, 360]$ on Thursday and $[90, 120]$ on Friday, the length and the start value of this region become smaller as d increases, because the number of end-of-day deliveries becomes less as it is closer to the end of the week. Similarly, for considered values of m, the region of z^d for the robust action $a = \{(1,1), \cdots, (1,1)\}$ (collect all blood for cryo) is approximately $[995, 1000]$ on Tuesday, $[900, 1000]$ on Wednesday, $[600, 1000]$ on Thursday and $[250, 1000]$ on Friday, and the length of this region becomes larger as d increases, while the start value becomes smaller, because the number of mid-day pickups becomes less as it is closer to the end of the week.

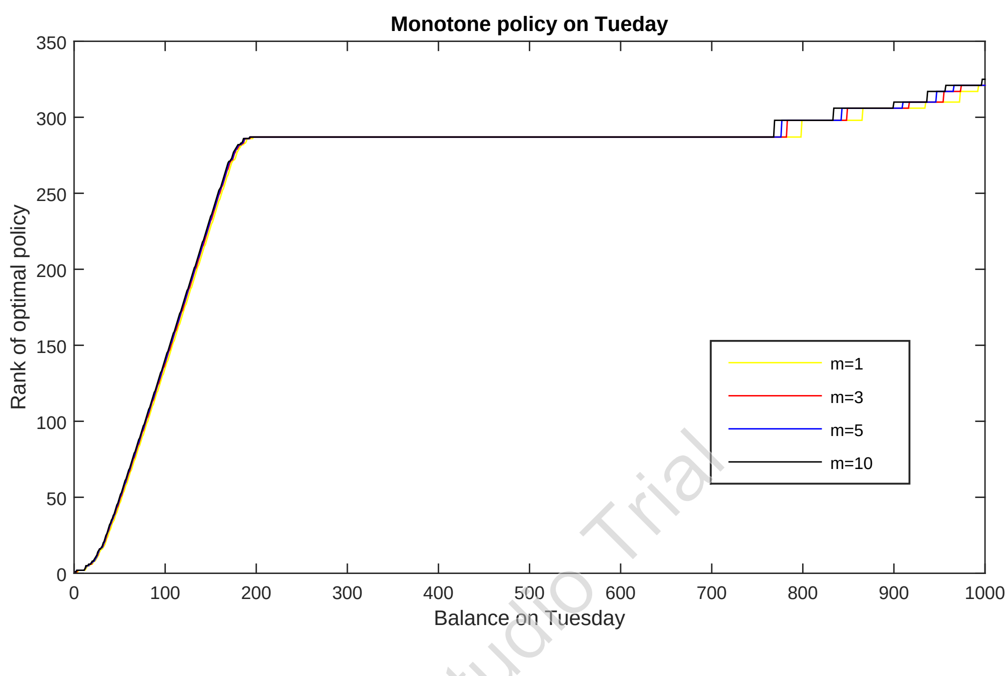


Figure 6: Actions on Tuesday

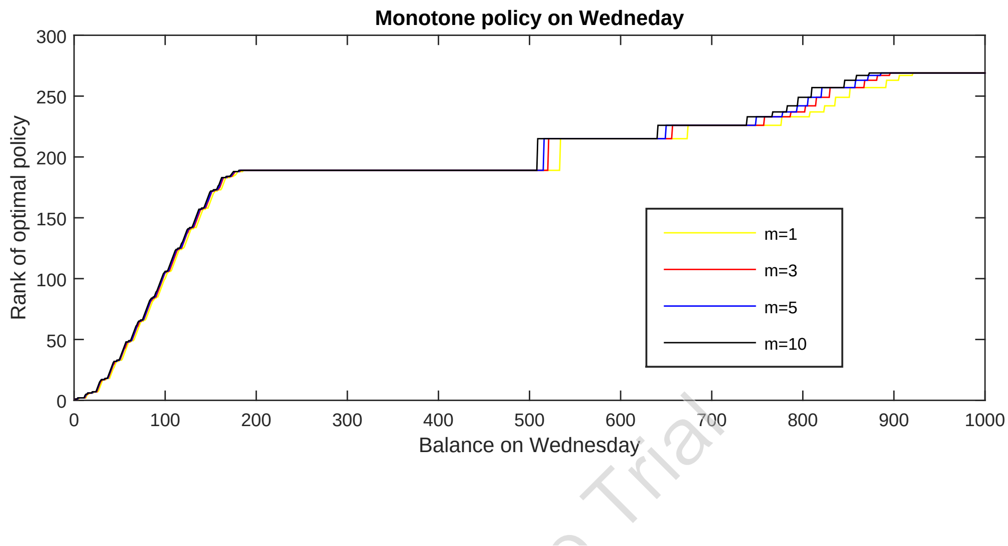


Figure 7: Actions on Wednesday

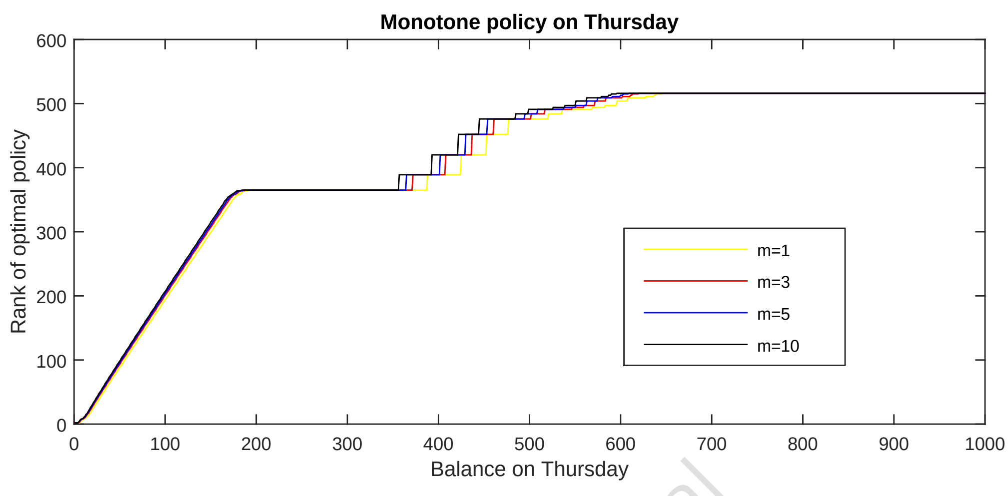


Figure 8: Actions on Thursday

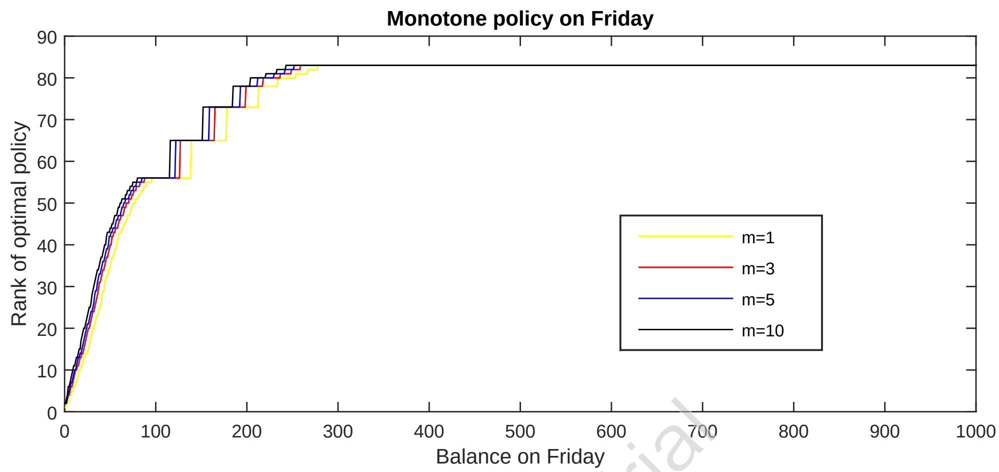


Figure 9: Actions on Friday

4.2.5 One-stage Chance Constrained Problem

For the one-stage stochastic optimization with the chance constraint, we numerically compare the performance of IP1.0 with Heuristic 2.0 in Table 10 for the split case. We remark that IP1.0 gives an optimal policy, while Heuristic 2.0 (only run the algorithm of Heuristic 2.1 on Monday) does not. Both policies are open-loop and can be used as a benchmark to compare with the policy from the rolling horizon decision making.

Table 10: IP1.0 vs. Heuristic 2.0

Split	IP1.0		Heuristic 2.0	
Week	Cost	P	Cost	P
1	\$777.94	4.94%	\$786.21	4.17%
2	\$655.69	4.65%	\$707.96	2.39%
3	\$935.84	4.94%	\$985.46	3.07%
4	\$673.34	4.94%	\$674.31	3.85%

Note. $P : P(z^6 > 0)$.

From Table 10, Heuristic 2.0 gives a sub-optimal policy, but the quality of policy is not always good, for example, the policy does not work as good as IP1.0 in week 2 and 3 in terms of the cost. Since IP1.0 gives the optimal policy for the one stage problem, we use it as a benchmark (an upper bound on the expected cost) for the sub-optimal policy from the rolling horizon decision making (IP1.1, IP1.2 and Heuristic 2.1) in the following section.

4.2.6 Multi-stage Chance Constrained MDP

For the split case, we numerically compare the performance of the rolling horizon decision making with the one-stage decision making, i.e., compare the performance of two IP based heuristics (IP1.1 and IP1.2) and the greedy heuristic (Heuristic 2.1) with IP1.0. We note that IP1.1 and IP1.2 use the policy by IP1.0 with minor modification each time period, and Heuristic 2.1 is a greedy algorithm that takes the advantage of fact that the end-of-day delivery is a free ride and the mid-day pickup cost is the major cost. We first show that we can adjust τ to find the sub-optimal policy and ensure the probability of missing the target is under 5%, then compare the performance of 4 algorithms.

Adjusting τ to find the sub-optimal policy: Since some states can be infeasible in a stochastic optimization problem with the chance constaint, we allow changing the value of τ to find the sub-optimal policy. Table 11 shows the performance of Heuristic 2.1 by different values of τ.

Table 11: Heuristic 2.1 by different τ

Split	$\tau = 0.95$		$\tau = 0.96$		$\tau = 0.97$		$\tau = 0.98$	
Week	Cost	P	Cost	P	Cost	P	Cost	P
1	\$644.37	6.77%	**\$671.58**	**3.82%**	\$684.70	2.93%	\$703.55	1.98%
2	**\$567.57**	**3.84%**	\$577.53	3.08%	\$589.02	2.38%	\$604.02	1.69%
3	\$768.68	5.57%	**\$781.51**	**4.59%**	\$796.98	3.66%	\$815.94	2.84%
4	\$568.07	5.18%	**\$576.55**	**4.40%**	\$587.50	3.55%	\$600.96	2.75%

Note. $P : P(z^6 > 0)$. Bold values are the best expected cost and probability of missing target.

Given τ, Heuristic 2.1 takes about 20 seconds to generate and evaluate the policy. From Table 11, we can simply find the sub-optimal policy by adjusting τ around 0.95. As τ increases, the weekly target becomes more important, and thus the expected cost increases as well as the probability of meeting the target. The sub-optimal poicy can also be obtained similarly by changing α ($\alpha = 1 - \tau$) in IP1.1 and IP1.2.

Rolling horizon decision making: We now show the numerical results of three rolling horizon decision making algorithms (IP1.1, IP1.2 and Heuristic 2.1), and compare them with IP1.0.

Table 12: Rolling horizon decision making

Split	IP1.1		IP1.2		H2.1		IP1.0	
Week	Cost	P	Cost	P	Cost	P	Cost	P
1	\$691.56	4.78%	**\$667.25**	**4.98%**	\$671.58	3.82%	\$777.94	4.94%
2	\$572.53	4.84%	**\$560.34**	**4.98%**	\$567.57	3.84%	\$655.69	4.65%
3	\$796.07	4.97%	\$783.76	4.97%	**\$781.51**	**4.59%**	\$935.84	4.94%
4	\$585.81	4.91%	**\$549.31**	**4.99%**	\$576.55	4.40%	\$673.34	4.94%

Note. $P : P(z^6 > 0)$. Bold values are the best expected cost and probability of missing target.

From Table 12, IP1.2 always results in the best sub-optimal policy, while Heuristic 2.1 is comparatively good. Overall, the rolling horizon decision making has better performance than the one-stage decision making (IP1.0), because it can delay determining the daily collection plan (a^d) and adjust it by the actual collection schedule (subject to $a \leq a^d$) to better utilize the updated information.

By the IP composition, the computational time of IP1.1, IP1.2 and Heuristic 2.1 are 40 minutes, 2 minutes and 2 minutes, respectively. IP1.1 takes a long time to evaluate the policy, however, its performance is not better than Heuristic 2.1. The reason is analyzed in Section 3.4.5, and IP1.2 is to deal with the drawback of IP1.1. In the following section, we compare all heuristics, and propose that we implement Heuristic 2.1 in practice.

4.2.7 Heuristics Comparison

In this section, we compare the proposed heuristics (Heuristic 1.3, Heuristic 2.1 and IP1.2) with respect to the total expected collection costs, computational time and overhead cost (whether it needs another software). For simplicity, we only consider the split case. Table 13 shows the average cost, computational time and whether it needs an IP solver for the 4 weeks in March 2012.

Table 13: Heuristics comparison

Comparison	Average cost	Computational time	Need a solver?
Heuristic 1.3	\$630.97	$\sim$ 10 hours	No
Heuristic 2.1	\$649.30	$\sim$ 2 minutes	No
IP1.2	\$640.17	$\sim$ 2 minutes	Yes

From Table 13, Heuristic 1.3 has the lowest average cost, however, its computational time is too much. IP1.2 is slightly better than Heuristic 2.1 in terms of the cost, however, it requires an IP solver. Since most IP solvers, such as CPLEX, are not free, Heuristic 2.1 is recommended in our practice. We will show in Section 4.4 that for both the non-split and the split cases, Heuristic 2.1 results in better or comparable total expected costs compared with Heuristics 1.1 through 1.3, while requiring significantly less computational time (only 2 minutes). Heuristic 2.1 also provides a key managerial insight that ranking the collection windows (for the non-split case) or the intervals (for the split case) by the mid-day pickup cost per unit of cryo and scheduling cryo sites following this ranking results in a competitive near-optimal solution. Comparing Heuristic 2.1 with Heuristics 1.1-1.3 for which we had analytical bounds, and discussing these results with the ARC management team led to the conclusion that Heuristic 2.1 was competitive enough and resulted in the development of a decison suppor tool (DST) that is currently being used by the ARC. In the following section, we compare Heuristic 2.1 performance against actual policies and characterize the impact in real practice.

4.3 Decision Support Tools

4.3.1 Impact in Practice

We now compare the results of Heuristic 2.1 (both non-split and split versions) to the actual costs accrued in order to estimate potential cost savings. As shown in Table 14, Heuristic 2.1 is expected to reduce the total cost by 29-48% for the non-split and by 73-85% for the split case, which were deemed very significant by the ARC management team.

Table 14: Cost comparison for Heuristic 2.1 (non-split and split) vs. the actual policy

Heuristic	2.1 non-split			2.1 split			Actual Policy
Week	decrease	Cost	E[cryo]	decrease	Cost	E[cryo]	Cost
1	34.03%	$1963.9	1121	77.44%	$671.58	1206	$2977
2	35.13%	$1709.9	1135	78.47%	$567.57	1155	$2636
3	29.28%	$2058.8	1135	73.15%	$781.51	1130	$2911
4	48.08%	$1953.7	1140	84.68%	$576.55	1130	$3763

Notes. decrease:% decrease in cost. $E[cryo]$: expected number of total cryo units collected.

The non-split version of the DST is currently being used by ARC for decision support and is in an informal testing phase. While the split version has a greater potential for reducing the total costs, it will require operational change before being implemented in practice. It is our understanding that the ARC team plans to first implement the non-split version of the DST, and gradually make the operational changes needed prior to moving to the split version. During the initial phase of implementation, the ARC Southern RMSC management became aware of several benefits of the DST. As an example, the DST identified sites to designate as cryo sites that had been excluded from consideration in the past. After a careful review, these sites are now considered as potential cryo collection sites. The impact of broadening the pool of sites for consideration as cryo sites has been significant. During the time of the initial introduction of the tool, demand and various factors required management to increase the cryo goal at the Southern RMSC. Using the tool, management was able to achieve an estimated 25% increase in the quantity of cryo produced with limited collection cost increase. While longer-term use is necessary to do a formal assessment, the ARC management was very pleased with the improvement in their current operations. The next steps include extensively testing the results from both the non-split and split versions of the DST in practice and making the corresponding operational changes gradually over time.

4.3.2 Decision Support Tool

We have built an MS Excel-based decision support tool (DST) based on the non-split and split versions of Heuristic 2.1. This DST was built in close collaboration with the ARC management team to ensure its practical use. The inputs to the DST included site information (region, date of collection, status, account number and name, address, shift start date, shift end date), mid-day transport cost for each site based on the zip code set by the courier, projected amount of collections for each site, the weekly target for cryo collection, probability of hitting the target, average speed of the delivery truck or time to deliver, penalty for same day collections, the option to include or exclude Saturday collections, and actual amount of collections at the end of each day (see Figures 10 and 11). The exact distance of each site from the RMSC was calculated using Google maps based on the collection site and RMSC addresses. The tool re-optimized the collection schedules after the realization of each day's total collection, and also gave the option of manually changing some of the scheduled sites and re-optimizing accordingly. A user's guide for the DST is delivered to the ARC and is available upon request.

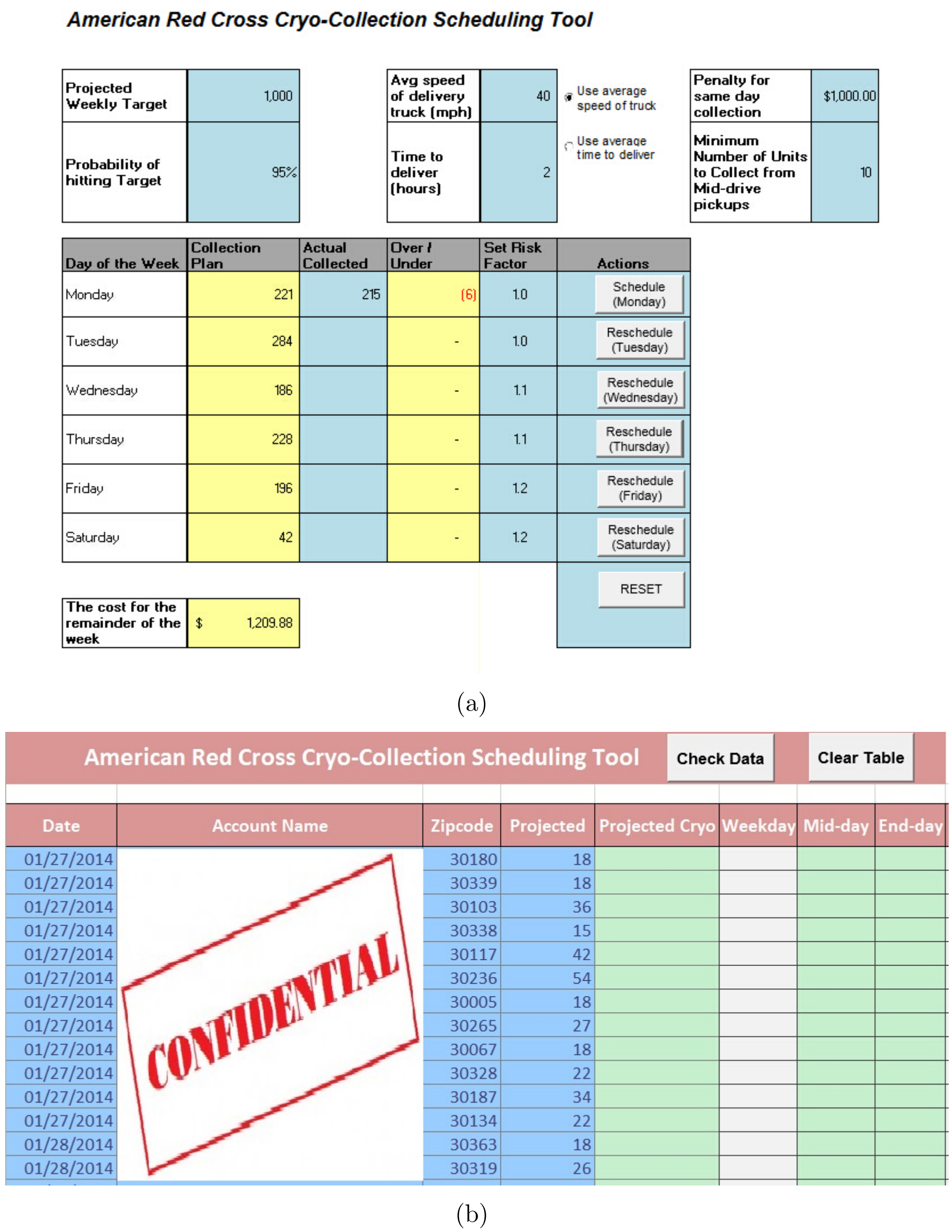
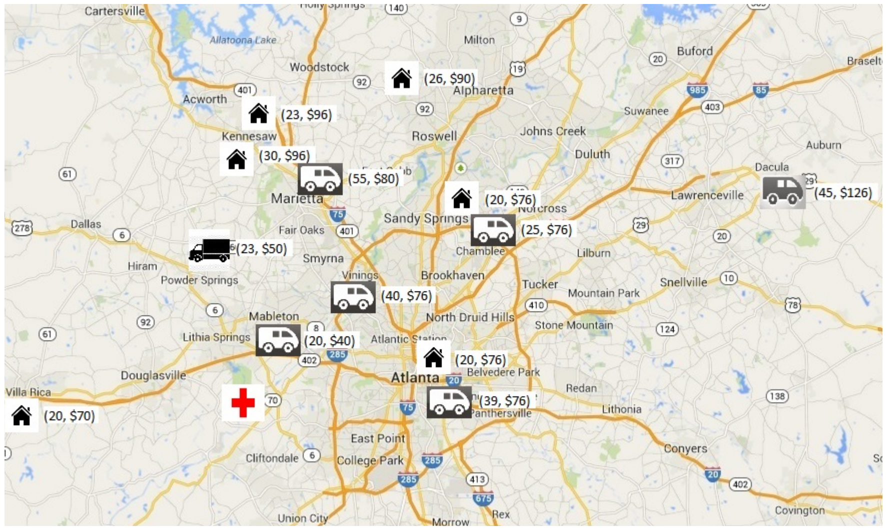
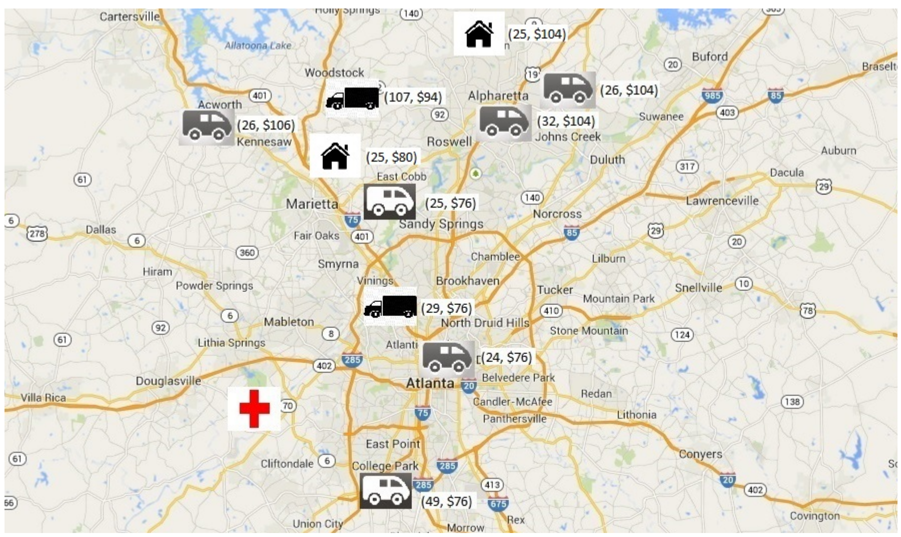


Figure 10: Screen shots from the Cryo-collection DST.

Now we demonstrate the performance of the non-split version of the DST in comparison with the actual policy. Figure 11 illustrates the collection schedules generated by the non-split version of the DST and the actual policy for Monday, March 5, and Wednesday, March 7, 2012. On Monday, there were 13 sites, of which 5 were designated as cryo sites only by the DST (white vans), 1 only by the actual policy (gray



(a) Monday



(b) Wednesday

Figure 11: Collection schedules by Heuristic 2.1 and actual policy for selected days.
Notes. The cross represents the ARC Southern RMSC, white vans represent sites designated as cryo sites only by the DST, gray vans represent sites designated as cryo sites only by the actual policy, black trucks represent sites designated as cryo sites both by the DST and the actual policy, and black buildings represent sites not designated as cryo sites by both the DST and the actual policy. The expected blood collection amount and mid-day pickup cost are shown in the parenthesis.

vans), 1 by both (black truck), and 6 by none (black buildings). The total amount of cryo units collected and total mid-day pickup costs were 173 and $419 for the DST and 78 and $175 for the actual policy. On Wednesday, there were 10 sites, of which 2 were designated as cryo sites only by the DST, 4 only by the actual policy, 2 by both, and 2 by none. The total amount of cryo units collected and total mid-day pickup costs were 249 and \$353 for the DST and 254 and \$714 for the actual policy. Hence, the DST generates the policy that results in a lower mid-day pickup cost per cryo unit collected.

Other than providing operational decision making by this DST, we also consider a strategic decision making in the following section.

4.4 Recommend Split Model

We now provide a comprehensive analysis of two cryo collection models, that is, we compare the non-split case (what ARC currently do) with the split case (what we recommend them to do) and estimate the benefit of using the split collection model to improve the cryo collection. We start by showing the numerical results of Heuristic 1.1-1.3 and Heuristic 2.1, then analyze the benefits of applying the split model, and conclude. We note that the decision making is at the strategic level and is the key factor to save the cost.

The non-split case: Table 15 presents the expected triple bag and mid-day pickup costs $\bar{u}_1^1(z^1)$ and $P(z^6 > 0)$ for Heuristics 1.1 through 1.3 and 2.1 for the non-split case. computational times are on the order of 10 minutes, 4 hours, 8 hours, and 2 minutes for Heuristics 1.1, 1.2, 1.3, and 2.1, respectively.

The split case: Table 16 presents the expected triple bag and mid-day pickup costs $\bar{u}_1^1(z^1)$ and $P(z^6 > 0)$ for Heuristics 1.1 through 1.3 and 2.1 for the split case. computational times are on the order of 10 minutes, 5 hours, 10 hours, and 2 minutes for Heuristics 1.1, 1.2, 1.3, and 2.1, respectively.

Table 15: Expected total costs and probability of missing the weekly target for Heuristics 1.1-1.3 and 2.1: non-split case

Heuristic	1.1		1.2		1.3		2.1	
	Cost	P	Cost	P	Cost	P	Cost	P
Week 1	$1988.6	4.49%	$1953.0	4.77%	$1953.2	4.69%	$1963.9	4.94%
Week 2	$1725.0	3.69%	$1695.5	4.13%	$1697.5	3.95%	$1709.9	4.37%
Week 3	$2084.6	3.31%	$2055.5	3.48%	$2056.4	3.41%	$2058.8	4.63%
Week 4	$1955.8	3.71%	$1953.5	3.72%	$1934.0	3.75%	$1953.7	4.08%

Note. $P : P(z^6 > 0)$.

Table 16: Expected total costs and probability of missing the weekly target for Heuristics 1.1-1.3 and 2.1: split case

Heuristic	1.1		1.2		1.3		2.1	
	Cost	P	Cost	P	Cost	P	Cost	P
Week 1	$691.16	4.44%	$649.62	4.67%	$649.13	4.61%	$671.58	3.82%
Week 2	$597.68	3.59%	$564.58	3.66%	$559.52	3.74%	$567.57	3.84%
Week 3	$807.46	3.49%	$777.93	3.60%	$777.55	3.57%	$781.51	4.59%
Week 4	$557.22	4.91%	$540.00	3.30%	$537.69	3.31%	$576.55	4.40%

Note. $P : P(z^6 > 0)$.

Non-split case and split case: Based on the numerical results, we've seen a huge reduction of expected cost in the split case, we now analyze why the split model is better.

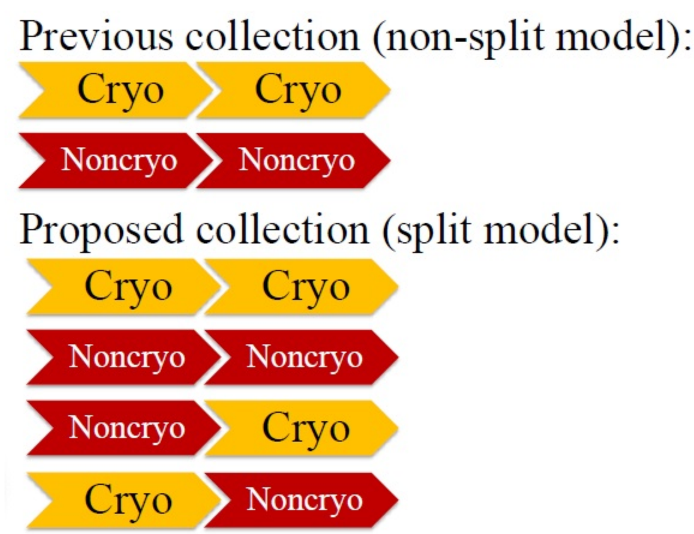


Figure 12: Comparison of two collection models.

As shown in Figure 12, the split model has two more options of blood collection for a site, one of which (collect noncryo first and then cryo) permits some blood collected in the second interval is processed to cryo without a mid-day pickup, that is, transporting the blood collection of second interval back to ARC is a backhaul with no extra transportation cost, and thus this collection saves transportation cost. Given that additional cryo bag cost is very small ($0.13 per bag), and the transportation cost is the major cost ($40-$120 for one mid-day pickup), our proposed split model can save a lot of transport cost and thus improve the cryo collection.

CHAPTER V

CONCLUSION

We summarize the problem considered and the results obtained in this dissertation in Section 5.1. In particular, we summarize the cryo collection problem and the methodologies for determining solutions to the problem, including a relaxation technique, structural policy and action elimination results, and several heuristics. We then use one of the heuristics to build a practical decision support tool. We also show that the split model concept can significantly reduce the cost of collection without sacrificing the likelihood of achieving the weekly target. We present topics for future research in Section 5.2.

5.1 Summary

In this dissertation, we have modeled the cryo collection problem as an MDP with a terminal cost and as an MDP with a chance constraint. We have analyzed these two models in order to achieve two goals: (1) minimize the expected cost of collecting cyro and (2) insure that the weekly cryo production target is achieved with a probability deemed acceptable by the ARC management. We also have considered two variants of the cryo problem: (1) the current collection process (the non-split case) and (2) the proposed collection process (the split case), and we have determined the impact on expected cost that would occur if the proposed collection process were to replace the current collection process.

We faced two constraints in modeling and analyzing the cryo collection problem. First, cryo has a tighter collection-to-completion constraint (8 hours) than the other blood products (24 hours). mid-day pickups, at additional expense, are often required in order to insure that the cryo collection-to-completion constraint is satisfied for blood collected in the first half of the collection window to insure that the weekly collection target is achieved with sufficiently high probability. The challenge created by this constraint is to determine policies that minimize the expected cost of mid-day pickups and triple bags. Second, collection windows (for the non-split case) or the intervals of these windows (for the split case) must be designated as cryo or non-cryo windows or intervals at least two days in advance of the actual collection day in order to insure that the boxes in which the blood collection bags are stored on the blood mobiles can be packed with the proper type of bag.

The cryo problem is naturally modeled as a finite-horizon MDP. The first constraint motivated modeling mid-day pickups, and the second constraint required state space augmentation. The state space augmentation produced an MDP with significant computational challenges. These challenges were magnified when we considered the split case. Propositions 1, 2 and 3 enabled significant reduction in computational demands, although not to the point of tractability for real world problems.

We first considered the MDP model with a penalty function, using the penalty function to indirectly assure that the chance constraint was satisfied. We took this indirect approach to satisfy the chance constraint knowing that an MDP with a terminal cost would not violate the Principle of the Optimality and that an MDP with a chance constraint might violate the Principle of the Optimality. The value of not violating the Principle is that the decomposition of the problem into the optimality equations is guaranteed to be useful in determining an optimal policy.

We developed a relaxation model which provides a lower bound using Proposition 4.

Relaxing the second constraint, we used Propositions 5 and 6 to determine a computationally tractable procedure for finding a lower bound on the optimal expected cost function. We then used this lower bound to determine a sub-optimal policy. A simple, quite conservative procedure was developed to insure that this sub-optimal policy was feasible, i.e., that the bloodmobiles were loaded with the right bags in order to satisfy the second constraint. This procedure benefitted from the fact that the difference in the cost of the two types of blood collection bags is small. We then were able to (i) determine an upper bound on the optimal expected cost function (Proposition 7) and (ii) determine an analytical expression of the difference between the upper and lower bounds (Proposition 8). We then adjusted the terminal cost function to ensure that the chance constraint is met. We named the resulting heuristic Heuristic 1.1 and developed improved variations of Heuristic 1.1, calling them Heuristics 1.2 and 1.3. Additional structural results (Lemma 2, Corollaries 3 and 4) are introduced to further improve the computational time when finding optimal policies under multiple penalty functions. Numerical results showed that these heuristics generated good sub-optimal policies.

We then considered an alternative model, the MDP model with chance constraint. This model represents a more direct way of modeling the cryo problem. However, we are no longer guaranteed that DP will provide an optimal policy, as illustrated by a counter example. Thus, although the MDP with a chance constraint is a more natural model of the cryo collection problem, it inherits significant computational challenges. Our approach for dealing with these challenges was to consider a sequence of single stage chance constrained problems, each associated with a day of the week and dependent on the number of cryo units that need to be collected for the remainder of the week in order to fulfill the weekly cryo collection target. We solved each of these single stage chance constrained problems using integer programming (IP). We named this heuristic IP1.1 and its improved variation IP1.2 and showed that IPI.2 generated very competitive policies compared with Heuristics 1.1 and 1.3. However, IP1.1 and IP1.2 require an IP solver, a drawback for implementing IP-based heuristics.

We also presented another heuristic, Heuristic 2.1, for determining a sub-optimal policy for the cryo collection problem. Heuristic 2.1 is intuitive, computationally simple, and simple to implement. Numerical comparisons indicated that Heuristic 2.1 is quite competitive with Heuristics 1.1-1.3 and IP1.1-1.2 at producing a high quality sub-optimal policy. As a result, Heuristic 2.1 was ideal to serve as the basis of a decision support tool (DST). We remark that Heuristic 2.1 was proposed very early during our interactions with ARC; however, at the time there was no way to evaluate the quality of its solutions. Motivation for the development of the other heuristics was two-fold: (1) to develop heuristics based on optimization principles that hence had the potential of producing near-optimal solutions and (2) to serve as a basis for evaluating the quality of policies produced by Heuristic 2.1.

The technical and practical contributions of this dissertation are as follows:

Technically, we first developed procedures for generating sub-optimal policies for a specially structured large-scale finite-horizon MDP with terminal cost. We used a constraint relaxation technique and an action elimination procedure to determine a computationally tractable lower bound and sub-optimal policy. We determined an easily computable bound on the difference between the value of the sub-optimal policy and the lower bound, providing an analytic measure of sub-optimal policy quality. Procedures for improving the quality of this sub-optimal policy were then developed. Numerical procedures were used to adjust the terminal cost function of this MDP in order to insure that the resulting sub-optimal policy satisfied the chance constraint.

As an alternative approach for determining good sub-optimal policies, we then developed a sequence of single stage chance constrained problems in order to determine a sub-optimal policy. We developed an IP solution procedure to find an optimal policy for each single stage chance constrained problem. We also considered a simple-to-understand-and-implement greedy heuristic to generate sub-optimal policies and used the two procedures to determine the quality of policies produced by this greedy heuristic. We showed that this quality is in general quite close to the quality of the policies produced by some of the less computationally intensive heuristics based on the two aforementioned approaches for generating policies.

From an applications perspective, we provided the ARC with a DST that was based on the greedy heuristic for both the non-split and split cases. Our initial analyses indicated that the estimated potential cost savings from the greedy heuristic, relative to current operating procedures, are about 29-48% for the non-split case and 73-85% for the split case. The initial use of the non-split version of the DST in practice has provided important managerial insights, and has shown promise for significant improvements in current operations. In addition to the non-split version, which is being used in practice now, the ARC team also plans to test and then gradually implement the split version of this DST in the future to further reduce the total costs.

We remark that the quality of policies resulting from the MDP with a terminal cost model is in part due to the very small difference in cost between triple and double blood collection bags. Further, we note that the significant improvement in performance that would result in moving from the non-split case to the split case is due to the fact that the bloodmobiles return to the production facility at no additional cost and the split case uses this fact to its advantage.

5.2 Future Research

We now present topics for future research.

We have assumed in this research that a bloodmobiles collection window is divided into two intervals of equal length for the split case. Where the collection window is divided can be optimized in order to insure the mid-day transportation and the transport of blood units collected for cryo in the second interval transported by the bloodmobile satisfies the collection-to-completion constraint with the highest probability.

We have assumed that travel times of both the mid-day transport and the bloodmobiles are deterministic when in fact travel times are random and subject to traffic congestion, etc. Modeling the uncertainties associated with travel time and using routing algorithms to determine optimal routes would enhance model validity and decision support system performance.

In this research we have restricted a mid-day vehicle to make only one pickup. Allowing mid-day transportation vehicles to have more than one pickup stop could reduce mid-day transportation cost. The obvious trade-off that would result would be between mid-day transportation cost and the likelihood of violating the collection-to-completion constraint.

Design more efficient algorithms to find the best y^d for Heuristics 1.2 and 1.3. We used a simple, relatively inefficient linear search procedure.

Clearly, if management procedures at ARC could be changed so that the two-day constraint on packing the storage boxes prior to bloodmobile departure could be removed, the lower bound that we developed would then become the expected optimal cost for the cryo problem.

This research has focused on the collection process and has assumed away how this process can affect the efficiency of the down stream processes, e.g., the production processes. For example, when the mid-day vehicles and bloodmobiles return to the production facility affects the queue length of blood units waiting for processing and this can affect the likelihood of meeting the collection-to-completion constraint for cryo. Clearly, this queue should not be FIFO (First In, First Out). Assessing the impact of collection schedules on production facility productivity, the production of other blood products, and the distribution of processed blood products to customers is also a topic for future research.

Appendix: Proofs of the Analytical Results

Proof of Proposition 1. Proof follows from an induction argument and the following facts and assumptions: (i) v^6 is monotonically increasing in z, (ii) a monotone function of monotone function is monotone (i.e., if f and g are monotonically increasing functions, then $f(g(z))$ is also monotonically increasing), and (iii) the sum and minimum of monotone functions are monotone. $\square$

Proof of Proposition 2. Proof by contradition. If there exists an optimal daily collection plan $a = \{(\alpha_n, \beta_n)\}$ such that $\exists\, i$, *s.t.* $\alpha_i = 1, \beta_i = 0$, then consider another daily collection plan $a' = \{\alpha'_n, \beta'_n\}$ such that $\alpha'_j = \alpha_j$, $\beta'_j = \beta_j$ for all $j \neq i$, and $\alpha'_i = 0$, $\beta'_i = 1$. By Assumption 2, we have $P(D|a) = P(D|a')$.

It can be shown that $c(a', a') < c(a, a)$ because a' can save the mid-day pickup cost. This contradicts with the assumption that a is the optimal daily collection plan. Therefore, a cannot be an optimal daily collection plan, and thus cannot be an optimal actual collection schedule. $\square$

Proof of Proposition 3. Proof follows from an induction argument, the fact that $\{v^d\}$ is monotone from Proposition 1, and the following facts. Let $h(z, a^d, a, v) = c(a^d, a) + \sum_D P(D|a)v(z-D)$ and assume v is monotone, where v is a real-valued function of z. Let a, a' be such that $a \leq a^d$ and $a' \leq a^d$, where $a = \{\alpha_n, \beta_n\}$, $a' = \{\alpha'_n, \beta'_n\}$. Assume $\alpha_n = \alpha'_n$ for all n, $\beta_n \geq \beta'_n$ for all n. Thus, $c(a^d, a) = c(a^d, a')$ and $a' \leq a$. Recall that $P(D|a) = P(\sum_n(X_n\alpha_n + Y_n\beta_n) = D$. Let $\mathcal{Z} = \sum_n(X_n\alpha_n + Y_n\beta_n) = \mathcal{X} + \mathcal{Y}$, where $\mathcal{X} = \sum_n(X_n\alpha'_n + Y_n\beta'_n)$ and $\mathcal{Y} = \sum_n Y_n(\beta_n - \beta'_n)$. Note that $P(D|a) = P(\mathcal{Z} = D)$ and $P(D|a') = P(\mathcal{X} = D)$. By assumption, $\mathcal{X}$ and $\mathcal{Y}$ are independent and non-negative discrete random variables. From Lemma 4.7.2 ([60]) it is sufficient that $P(\mathcal{Z} \geq k) \geq P(\mathcal{X} \geq k)$ for all k in order that $h(z, a^d, a, v) \leq h(z, a^d, a', v))$ and hence

a' can be eliminated. Note for arbitrary k,

$$\begin{aligned}
P(\mathcal{Z} \geq k) &= \sum_{D \geq k} P(\mathcal{X} + \mathcal{Y} = D) \\
&= \sum_{D \geq k} \sum_{j=0}^{D} P(\mathcal{X} = j) P(\mathcal{Y} = k - j) \\
&= \sum_{j=0}^{k-1} P(\mathcal{X} = j) P(\mathcal{Y} = k - j) + P(\mathcal{X} \geq k),
\end{aligned}$$

and hence $P(\mathcal{Z} \geq k) \geq P(\mathcal{X} \geq k)$ for all k. $\square$

Proof of Proposition 4. Proof of the isotonicity of $\{\ell^d\}$ is analogous to the proof of the isotonicity of $\{v^d\}$ in the proof of Proposition 1. The inequalities follow directly for any v from an induction argument, the isotonicity of $c^d(a^d, a)$ in a^d, and the following inequalities:

$$\begin{aligned}
&min\{c^d(a, a) + \sum_{D} P^d(D|a) v(z - D) : a\} \\
\leq &min\{c^d(a, a) + \sum_{D} P^d(D|a) v(z - D) : a \leq a^d\} \\
\leq &min\{c^d(a^d, a) + \sum_{D} P^d(D|a) v(z - D) : a \leq a^d\}.
\end{aligned}$$

$\square$

Proof of Proposition 5. Since c_T is non-decreasing, it is sufficient to show for arbitrary t that if v_{t+1} is non-decreasing, then v_t is non-decreasing. For this result to hold, it is sufficient to show that $h_t(s, a, v)$ is non-decreasing in s for all a for any non-decreasing function v. We note that $v(f_t(s, a, d))$ is non-decreasing in s for all a and d since a non-decreasing function of a non-decreasing function is non-decreasing. Since the weighted sum of non-decreasing functions is non-decreasing, v_t is non-decreasing for all t.

Let action a dominate action a'. It is sufficient to show that for non-decreasing v, $h_t(s, a, v) \leq h_t(s, a', v)$ for all s and t. This inequality holds if $\sum_d p_t(d|a) v(f_t(s, a, d)) \leq$

$\sum_d p_t(d|a')v(f_t(s,a',d))$, which is guaranteed by Lemma 4.7.2 [60] and the fact that a non-decreasing function of a non-decreasing function is non-decreasing. $\square$

Proof of Proposition 6 Let a and a are such that $g(a) \leq g(a)$ and $s \leq s$, then $h_t(s,a,v_{t+1}) - h_t(s,a,v_{t+1}) \leq h_t(s,a,v_{t+1}) - h_t(s,a,v_{t+1})$, which holds by Lemma 4.7.2 [60] and additional assumptions. So, if $a_t^*(s) = a$, $a_t^*(s)$ has to be action a such that $g(a) \leq g(a)$. $\square$

Proof of Corollary 1 Proof follows dirctly by Proposition 4 and Proposition 5. $\square$

Proof of Corollary 2 Proof follows directly by Proposition 6, that function s here is the function g in the Proposition. $\square$

Proof of Lemma 1. Let the random variable Z be normally distributed with mean 0 and standard deviation 1. Then the result is equivalent to $P(Z \geq (\alpha - \mu')/\sigma') \geq P(Z \geq (\alpha - \mu)/\sigma)$ for all $\alpha \geq 0$. This inequality holds if and only if $(\alpha - \mu')/\sigma' \leq (\alpha - \mu)/\sigma$ for all $\alpha \geq 0$, which is equivalent to $\sigma'\mu - \sigma\mu' \leq \alpha(\sigma' - \sigma)$ for all $\alpha \geq 0$. Assumption 3 guarantees that the RHS of the latter inequality is non-negative for all $\alpha \geq 0$, Assumption 4, involving the coefficients of variation, guarantees that the LHS is non-positive, and hence the result holds. $\square$

Proof of Propositions 7, 8. Propositions 7 and 8 follow from a standard induction argument, the optimality equations for the lower bounds, and the definitions of $\{u^d\}$ and $\{\kappa^d\}$. $\square$

Proof of Proposition 9. Since $y^d = 0$ for all d gives the value of u^d, then $\bar{u}^d \leq u^d$ for all d. The result follows directly from Proposition 8. $\square$

Proof of Lemma 2 By summing the two inequalities we obtain

$$\sum_D P(D|\bar{a}')[v'(z-D) - v(z-D)] < \sum_D P(D|\bar{a})[v'(z-D) - v(z-D)]$$

If $c(\bar{a}') < c(\bar{a})$, then $s(\bar{a}') \leq s(\bar{a})$, as equivalently,

$$\sum_{D \geq k} P(D|\bar{a}') \leq \sum_{D \geq k} P(D|\bar{a}) \text{ for all } k.$$

Lemma 4.7.2 ([60]) implies

$$\sum_D P(D|\bar{a})[v'(z-D) - v(z-D)] \leq \sum_D P(D|\bar{a}')[v'(z-D) - v(z-D)],$$

which is a contradiction. Hence, $c(\bar{a}) \leq c(\bar{a}')$ □

Proof of Corollary 3. The assumptions of a_1 and a_2 imply that

$$h^d(z, a_1, \ell_1^{d+1}) \leq h^d(z, a_2, \ell_1^{d+1}),$$
$$h^d(z, a_2, \ell_2^{d+1}) \leq h^d(z, a_1, \ell_2^{d+1}).$$

and at least one of these inequalities is strict. Then Lemma 2 implies that $c^d(a_1, a_1) \leq c^d(a_2, a_2)$. □

Proof of Corollary 4. Assume $a^* \in \mathcal{D}^d(z, m)$ such that $h^d(z, a^*, \ell^{d+1}(\cdot, m)) < h^d(z, a', \ell^{d+1}(\cdot, m))$. Lemma 2 implies $c^d(a', a') = c^d(a^*, a^*)$. Since $a', a^* \in A^{ND}$, $s(a') = s(a^*)$, and hence we have a contradiction. □

Proof of Proposition 10. If a' is dominated by a^*, then by definition $c(a^*, a^*) \leq c(a', a')$, and $\sum_{D \geq k} P(D|a^*) \geq \sum_{D \geq k} P(D|a')$ for all k. Let $k = z^1$, then a' satisfies the chance constraint implies that a^* is also satisfied, and the cost of a' is no less than the cost of a^*. Therefore, it is not necessary to search dominated actions such as a'.

$\square$

Proof of Proposition 11. Given the distribution $D \sim Normal(\mu p^T a, \sigma^2 p^T a)$ where $p^T a$ is the projected cryo collection, then the chance constraint $P(z^6 > 0) = P(D < z^1) \leq \alpha$ is solving a quadratic inequality of $\mu p^T a - z_\alpha \sigma \sqrt{p^T a} \geq z^1 - 0.5$, where z_α is the upper 100α percentage point of the standard normal distribution and -0.5 is for continuity correction. Solving it we have $p^T a \geq (\frac{z_\alpha \sigma + \sqrt{(z_\alpha \sigma)^2 + 4\mu(z^d - 0.5)}}{2\mu})^2$. $\square$

Proof of Proposition 12. As α increases, z_α decreases, and thus the linear constraint associated with $p^T a$ is looser. The feasible region becomes larger, so the optimal cost decreases. $\square$

Proof of Lemma 3. The assumptions imply that $Y' = \sum_{j=1}^{J}(X_j - \mu_j)/\sqrt{\sum_{j=1}^{J}\sigma_j^2}$ is a standard normal random variable. Thus, $P(Y' \leq y(\tau)) \geq \tau$. By symmetry, $P(Y' \leq y(\tau)) = P(-y(\tau) \leq Y')$. Since $P(-y(\tau) \leq Y') = P(\sum_{j=1}^{J}\mu_j - y(\tau)\sqrt{\sum_{j=1}^{J}\sigma_j^2} \leq \sum_{j=1}^{J} X_j)$, $P(\sum_{j=1}^{J}\mu_j - y(\tau)\sqrt{\sum_{j=1}^{J}\sigma_j^2} \leq \sum_{j=1}^{J} X_j) \geq \tau$. Since $z \leq \sum_{j=1}^{J}\mu_j - y(\tau)\sqrt{\sum_{j=1}^{J}\sigma_j^2}$, $P(z \leq \sum_{j=1}^{J} X_j) \geq P(\sum_{j=1}^{J}\mu_j - y(\tau)\sqrt{\sum_{j=1}^{J}\sigma_j^2} \leq \sum_{j=1}^{J} X_j) \geq \tau$. $\square$

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